THE TOTAL SYNTHESES OF KAPAKAHINES E AND F: THE EVOLUTION OF THE DISCOVERY OF A UNIQUE REACTION UPON BROMOPYRROLOINDOLINES

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

The C(3)-quaternary substituted pyrroloindoline is a motif that is found in many natural products; therefore, a suitable methodology that can construct such a motif and has broad range and versatility is highly valuable. Discussed herein is the development of a novel method of the construction of C(3)-quaternary substituted pyrroloindolines and the application of the methodology to natural product synthesis.

A ring contraction of C(3)-bromo pyrroloindolines to form a highly strained cyclopropane intermediate allows for the direct addition of a wide range of nucleophiles to form valuable C(3)-quaternary substituted pyrroloindolines including C(3)-N(1′) heterodimeric indolines. The heterodimeric indolines synthesized using this method were then used in the total syntheses of Kapakahines E and F and toward a total synthesis of chetomin.

To Sharon Kirk

"That's How Strong My Love Is" - Otis Redding

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

[α]	specific rotation
Ac	acetyl
AIBN	2,2′-azobisisobutyronitrile
Ala	alanine
appt	apparent (spectral)
aq.	aqueous
atm	atmospheres (pressure)
bd	broad doublet (spectral)
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
Bn	benzyl
Boc, BOC	*tert*-butoxycarbonyl
BOPCl	bis(2-oxo-3-oxazolidinyl) phosphonic chloride
br	broad (spectral
bs	broad singlet (spectral)
bt	broad triplet (spectral)
bq	broad quartet (spectral)
Bu	butyl

*n*Bu	normal butyl
*s*Bu	secondary butyl
*t*Butyl	tertiary butyl
Bz	benzoyl
°C	degrees Celsius
calc'd	calculated
cat.	catalytic
Cbz	carboxybenzyl
conc.	concentration
COSY	correlation spectroscopy
*m*CPBA	*m*-chloroperoxybenzoic acid
CSA	10-camphorsulfonic acid
d	day(s); doublet (spectral)
DBAD	di-*tert*-butylazodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
dd	doublet of doublets (spectral)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
ddd	doublet of doublet of doublets (spectral)
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DIBAL, DIBAL-H	diisobutylaluminum hydride

dil.	dilute
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDC, EDCI	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EDG	electron donating group
ee	enantiomeric excess
EI	electron impact
eq., equiv	equivalents
ESI	electron spray ionization
Et	ethyl
EWG	electron withdrawing group
FAB	fast atom bombardment
g	gram(s)
h	hour(s)

HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	50% inhibitory concentration
imid	imidazole
IPCF	isopropenyl chloroformate
IR	infrared spectroscopy
J	coupling constant (NMR)
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LC	liquid chromatography
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LRMS	low resolution mass spectrometry
L-selectride	lithium tri-*sec*-butylborohydride
LUMO	lowest unoccupied molecular orbital

m	multiplet (spectral)
M	moles per liter
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry; molecular sieves
MTAD	*N*-methyltriazolinedione
m/*z*	mass to charge ratio
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
Ns	4-nitrobenzenesulfonyl
Nu	nucleophiles
Ph	phenyl
Phe	phenylalanine
Pin	pinacolato

PMB	*p*-methoxybenzyl
ppm	parts per million (NMR)
PPTS	pyridinium *p*-toluenesulfonate
*i*Pr	*iso*-propyl
*n*Pr	normal propyl
pro	proline
psi	pressure per square inch
N-PSP	*N*-phenylselenophthalimide
py	pyridine
q	quartet
[R]	reductant
R_f	retention factor (TLC)
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
rt	room temperature
s	singlet
sat.	saturated
SEMCl	2-(trimethysilyl)ethoxymethyl chloride
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDMS, TBS	*tert*-butyldimethylsilyl
Teoc	2-(trimethylsilyl)ethoxycarbonyl

TES	triethylsilyl
TESH	triethylsilane
Tf	trifluorosulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSI	trimethylsilyl iodide
TPP	tetraphenylporphyrin
Troc	2,2,2-trichloroethoxy carbonyl
Trt	trityl
Ts	*p*-toluenesulfonyl

LIST OF FIGURES

LIST OF TABLES

LIST OF SCHEMES

ACKNOWLEDGMENTS

My evolution as a chemist can be attributed to as many different and unique circumstances and people as there are stars in the sky, but only the most important of those will be announced here. First, I would like to thank my parents, Jose and Mary, for conceiving me…without which I would never have had the human experience; my sisters Raissa and Mischa, for always being wonderful even when at times there was no way I could have won brother of the year; all other relatives who believed in me, particularly, but in no particular order, uncle James, cousins Jennifer and Kanean, y mi abuelita Ana. Special thanks go to my undergraduate mentor, Michael Harmata, because without his guidance I would not have gone into the organic chemistry field that I love so much; my graduate advisor, Jon Rainier, for helping me speed through chemical problems with great swiftness. I would finally like to give appreciation to all of my colleagues that put up with my childishness on many an occasion…you know who you are.

CHAPTER 1

AN EXPEDIENT CONSTRUCTION OF C(3)-QUATERNARY SUBSTITUTED PYRROLOINDOLINES

Introduction

Pyrroloindolines with various atom substituents at the C(3)-position, including carbon, nitrogen, oxygen, etc., represent an incredibly diverse class of compounds that are ubiquitous in nature. The field of the isolation and synthesis of C(3)-substituted pyrroloindolines is quite remarkable as it has been an ongoing pursuit, both intellectual and practical, since before the 1930s. It has been a battleground for the testing of imaginative chemical transformations as well as bringing to the forefront of knowledge the inconceivable and breaking the consensus of what is thought impossible.

While a comprehensive review of C(3)-substituted pyrroloindolines is outside the scope of this dissertation, a representative field of examples of the stereoselective synthesis of natural products pertaining to C(3)-carbon, -oxygen, and -nitrogen substituted pyrroloindolines have been concisely documented in order to give the reader an inside view of the broad range of chemistry associated with this class of alkaloids. It is the wish of the author that the reader comes away with an appreciation of the beauty of pyrroloindoline alkaloid chemistry.

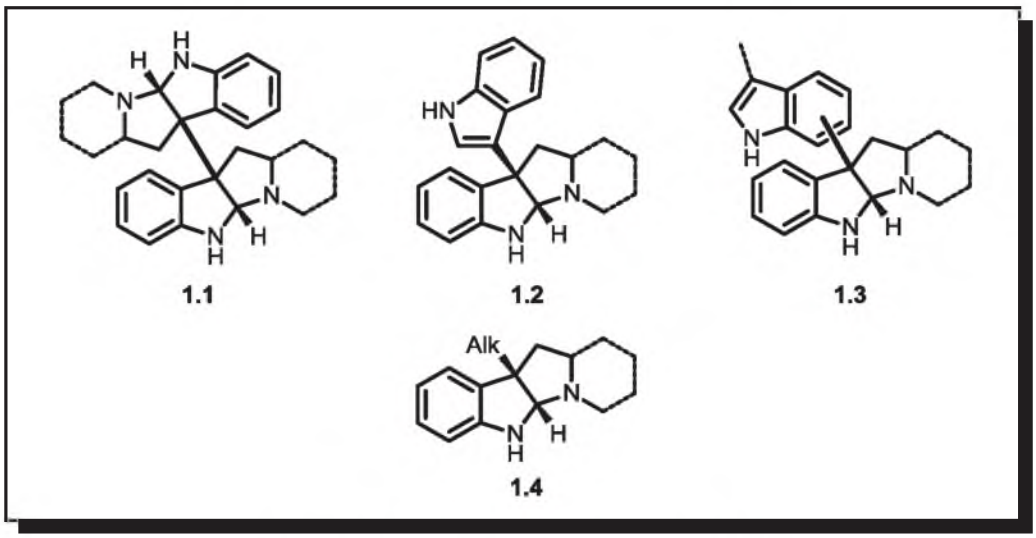
C(3)-Carbon Substituted Pyrroloindolines

Pyrroloindolines that are C(3)-carbon substituted are replete in nature and many synthetic methods have been developed in order to construct this bond. A representative array of this class of compounds is given in Figure 1.1 and includes dimeric and non-dimeric indolines.[1] A number of notable methods have been developed to address the issue of constructing C(3)-carbon substituted pyrroloindolines in the course of natural product synthesis.[2,3]

While brilliant methods had been devised toward the synthesis of C(3)-carbon substituted pyrroloindolines prior to the 1990s, there was a marked lack of enantioselectivity in these methods. Several total syntheses that display powerful stereoselective methods are deserving of mention and these include Danishefsky's syntheses of amauromine and ardeemin, Overman's syntheses of (+)- and (–)-chimonanthine, and Movassaghi's syntheses of (+)-chimonanthine and (+)-naseseazine A.[4,5,6]

Danishefsky's syntheses of amauromine and ardeemin showcase an oxidative cyclization of tryptophan derivatives with *N*-phenylselenophthalimide (*N*-PSP) and reverse prenylation of an activated C(3)-phenylseleno pyrroloindoline (Schemes 1.1-1.2).[4] The syntheses begin with a highly diastereoselective phenylselenocyclization of tryptophan **1.11** by reaction of the electrophilic selenium with the indole-[2,3]-π-bond to give pyrroloindoline **1.12** as essentially a single isomer in the *syn-cis* configuration.

General C(3)-Carbon Substituted Pyrroloindolines



Various C(3)-Carbon Substituted Natural Products

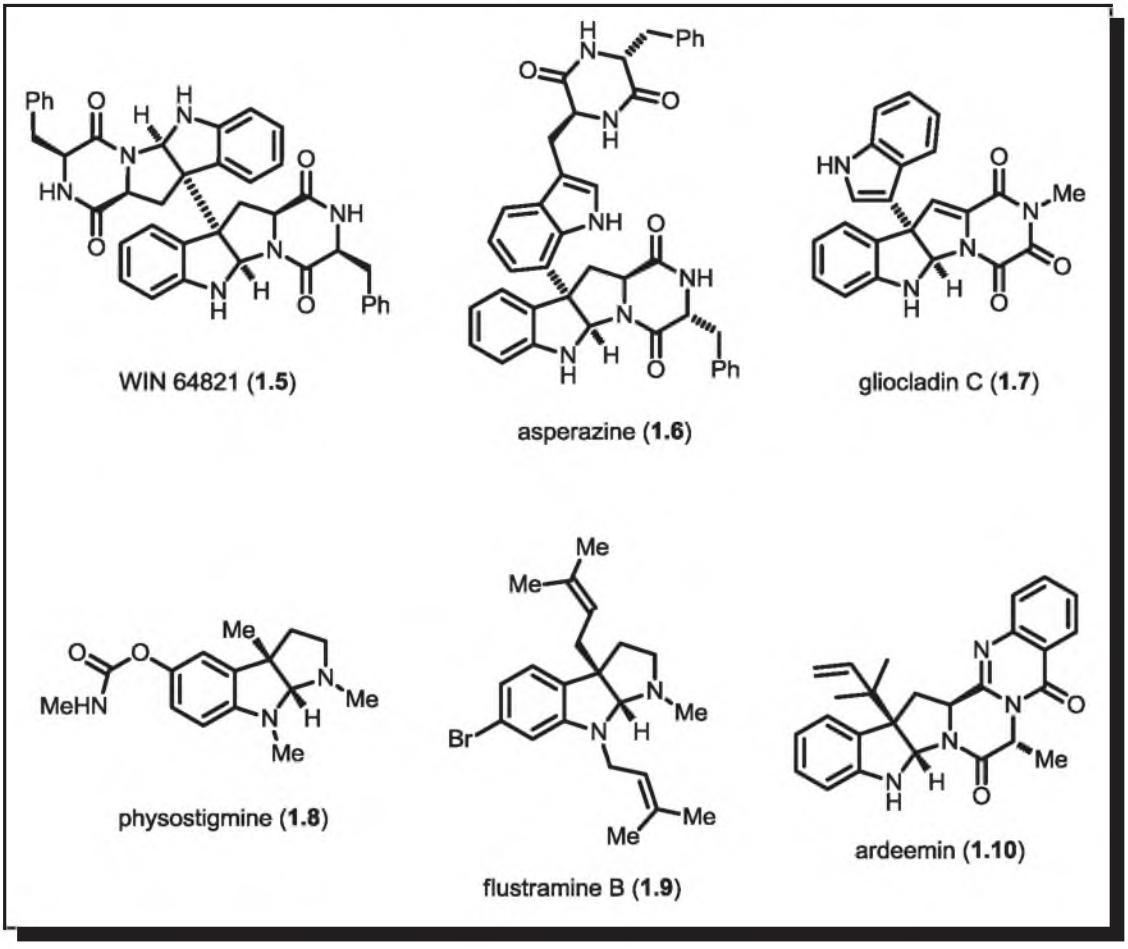
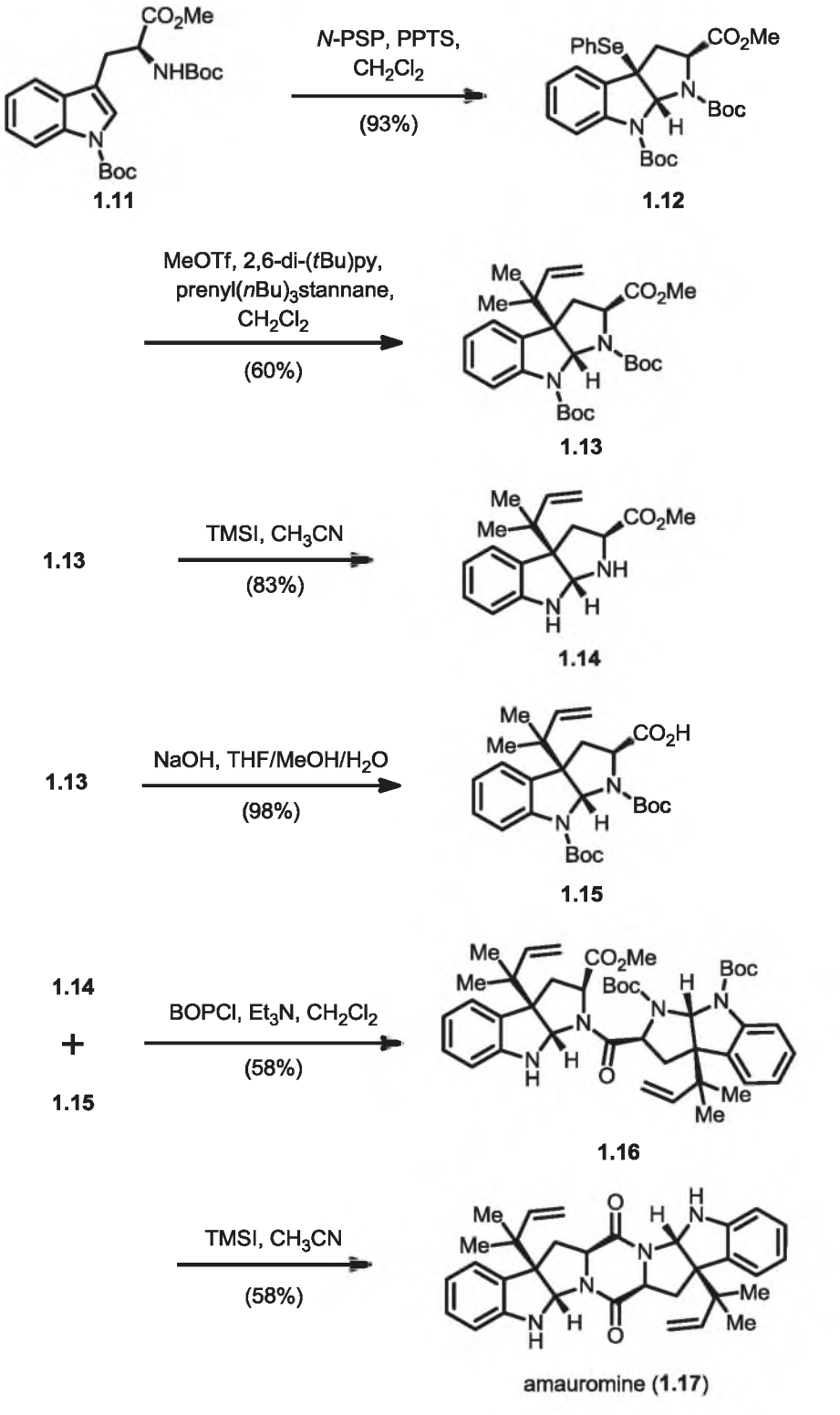
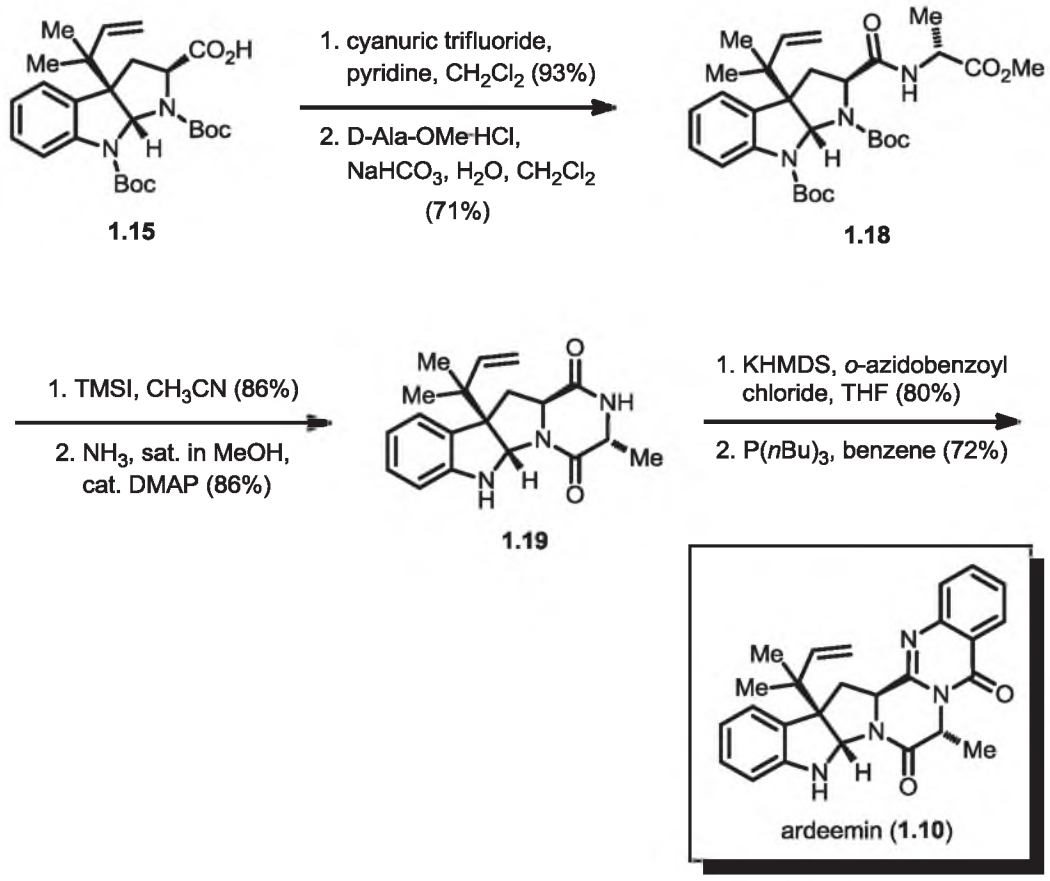


Figure 1.1. Representative C(3)-Carbon Pyrroloindolines



Scheme 1.1. Danishefsky's Total Synthesis of Amauromine



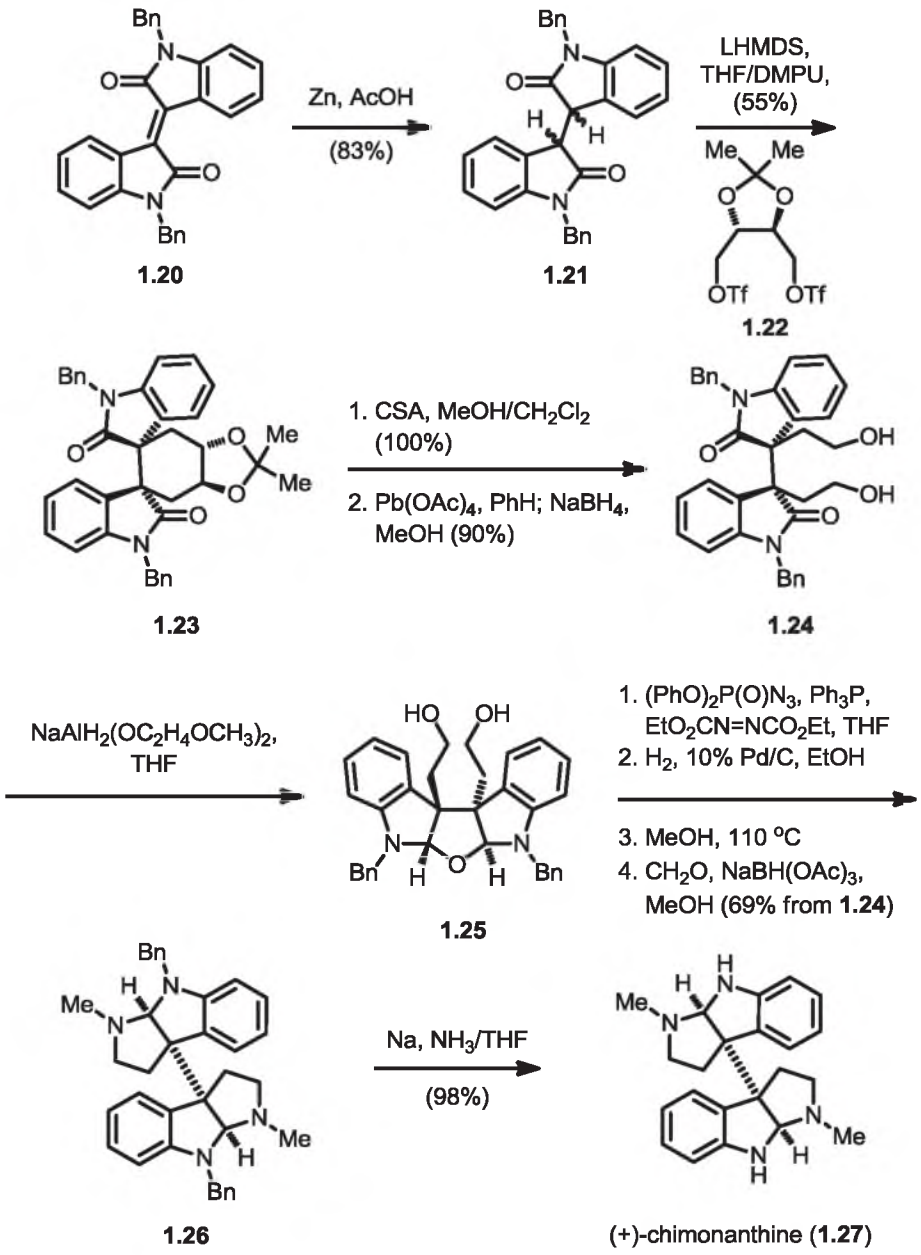
Scheme 1.2. Danishefsky's Total Synthesis of Ardeemin

The C(3)-phenylselenyl group was then activated with MeOTf to form a cationic selenium species that behaved as an excellent leaving group. This provided a transiently formed tertiary benzylic carbocation that was trapped by the prenyl nucleophile to give pyrroloindoline **1.13**. The pyrroloindoline **1.13** was then either hydrolyzed to give acid **1.15** or deprotected to give bis-amine **1.14** providing not only the starting material for the synthesis of ardeemin, but also the two subunits for the synthesis of amauromine. After peptide coupling between **1.14** and **1.15**, protecting group removal and subsequent diketopiperazine formation provides the natural product amauromine.

For ardeemin, the acid **1.15** undergoes a peptide coupling with alanine followed by deprotection and diketopiperazine formation to provide **1.19**. The synthesis was completed by benzoylation of the diketopiperazine followed by a Staudinger reaction to provide the natural product ardeemin. The syntheses required 6 and 10 steps overall from L-tryptophan methyl ester hydrochloride to amauromine and ardeemin, respectively.

The Overman group provided the first enantioselective synthesis of (+)-chimonanthine through the dialkylation of a metal dienolate with a tartrate derived electrophile that used the chirality of the tartrate moiety to control absolute stereochemistry (Scheme 1.3).[5b] The Overman group also developed a powerful intramolecular Heck reaction that allowed them to synthesize a number of natural products including (–)-chimonanthine and asperazine (Schemes 1.4-1.6).[5c,d]

Beginning with isoindigo **1.20**, Zn-mediated reduction gave oxindole dimer **1.21**. Alkylation of a di-metal enolate generated from **1.21** with bis-triflate **1.22** provided bis-spirooxindole **1.23** as the major isomer. Deprotection of the ketal with CSA and methanol followed by diol cleavage with lead tetraacetate and reduction of the bis-aldehyde with sodium borohydride provided diol **1.24**. Amide reduction with Red-Al gave **1.25**. Substitution of the diols with azide and reduction to a bis-amine cyclizes to a pyrroloindoline dimer after subjection to hot MeOH. Reductive methylation with formaldehyde then provided **1.26**, and finally benzyl group removal with sodium and ammonia in THF gave the natural product (+)-chimonanthine in 10 steps from isoindigo **1.20**.

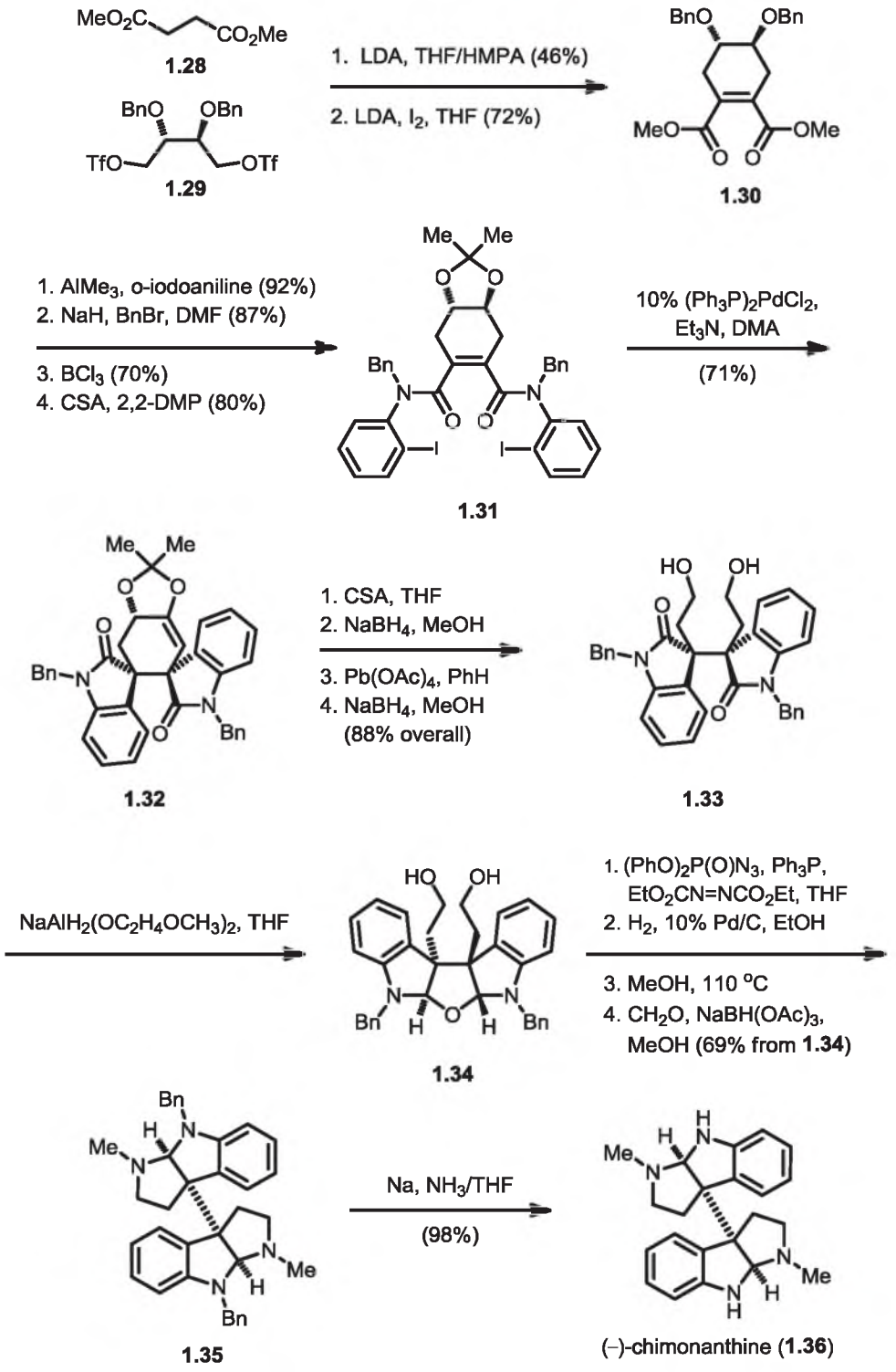


Scheme 1.3. Overman's Total Synthesis of (+)-Chimonanthine

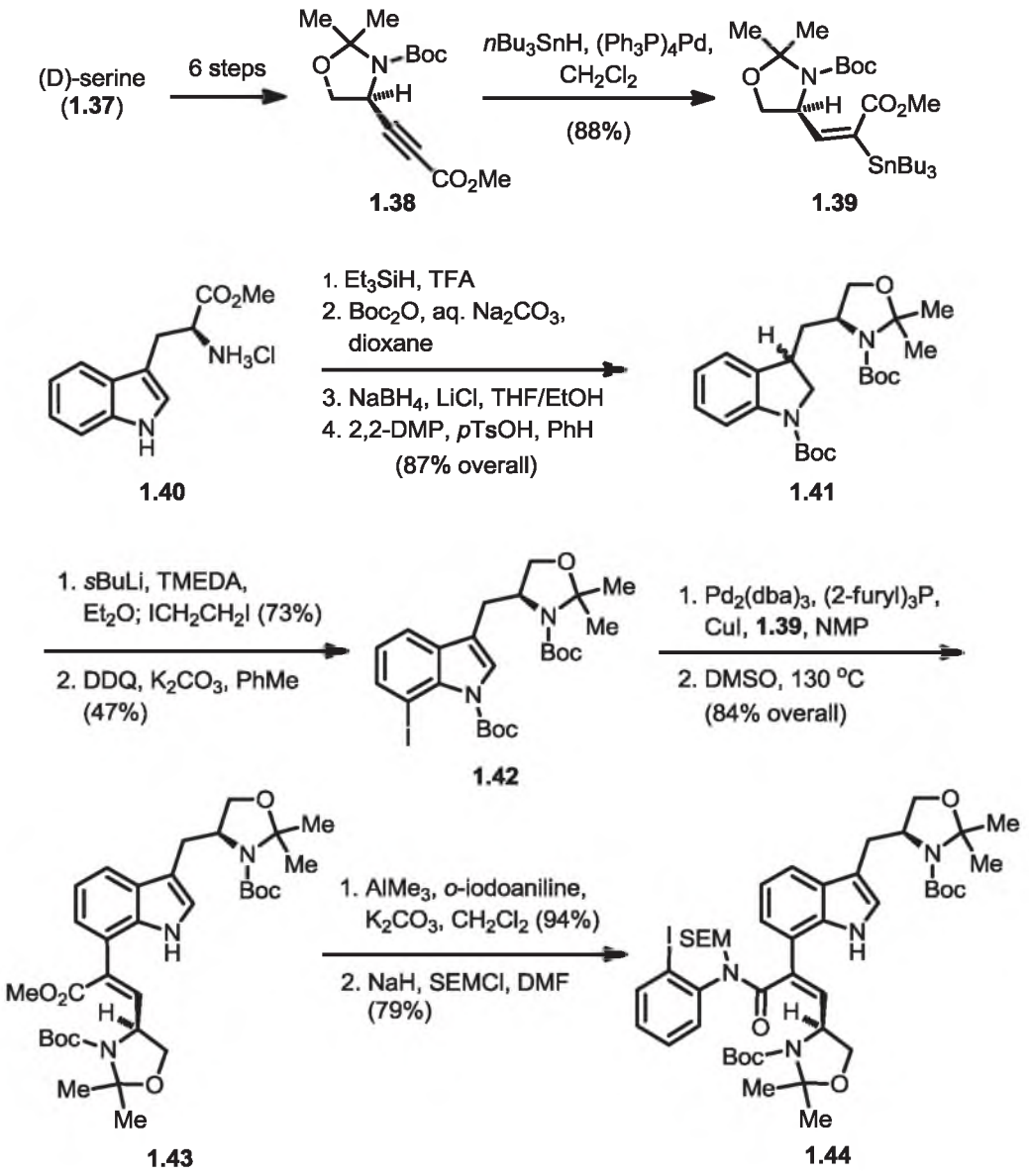
Overman's synthesis of (–)-chimonanthine employed a significantly different route.[5c] Starting with the coupling between the dimethyl succinate **1.28** and bis-triflate **1.29**, followed by iodination and elimination gave unsaturated diester **1.30**. Reaction with the aluminum amide of *o*-iodoaniline afforded the corresponding bis-amide. Benzyl protection of the amides followed by exchange of the benzyl ethers for an acetonide protecting group gave **1.31** that was ready for the intramolecular Heck cascade reaction. The palladium-catalyzed Heck reaction performed well with a single isomer being obtained as **1.32**.

Acetonide deprotection afforded a keto-alcohol that was reduced with sodium borohydride; the diol was cleaved to the corresponding dialdehyde and reduced to diol **1.33**. The same protocol that was used to transform diol **1.24** to (+)-chimonanthine (Scheme 1.3) was then used to transform diol **1.33** to (–)-chimonanthine (Scheme 1.4). The overall synthesis from **1.28** required 17 steps.

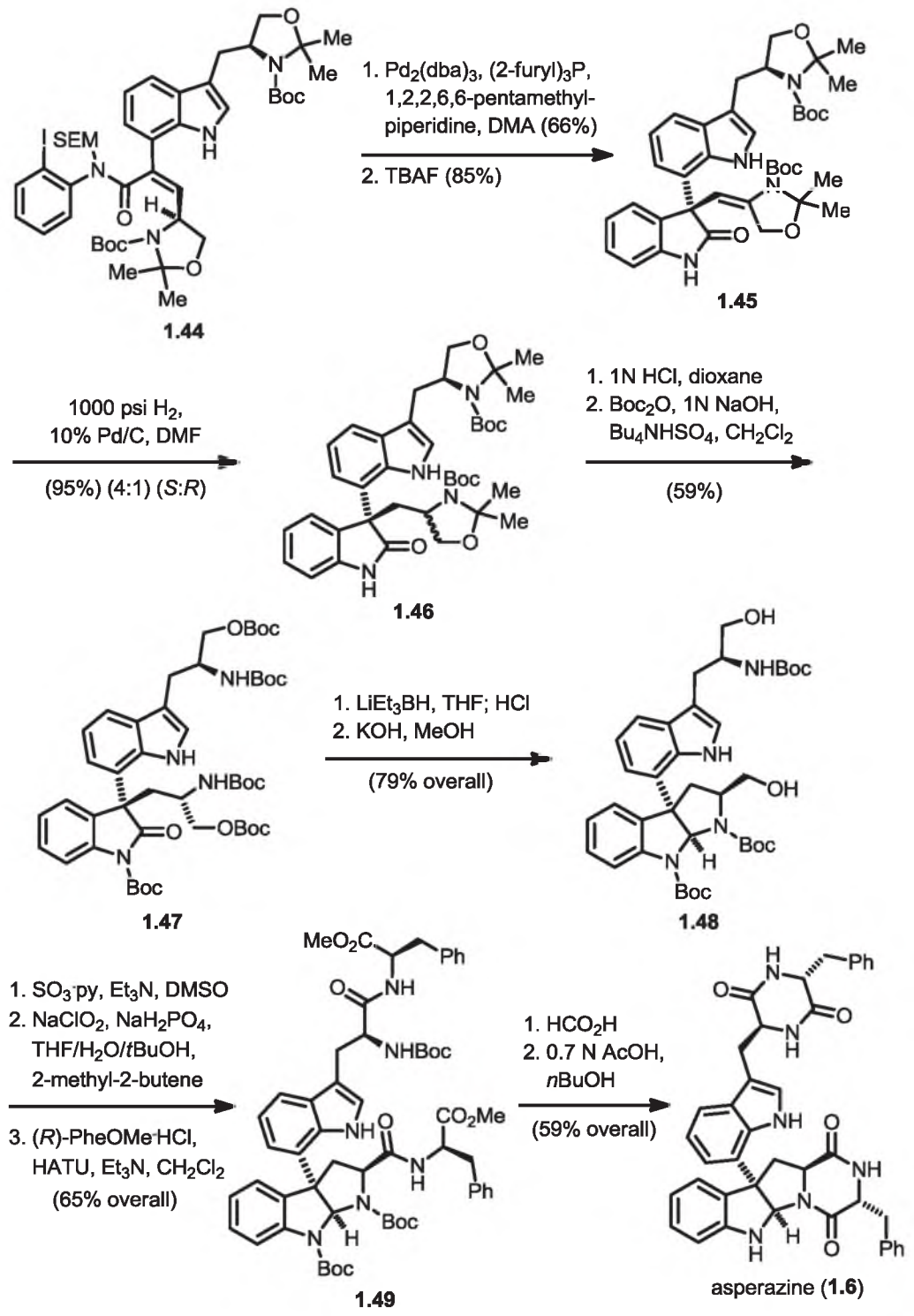
The power of the Heck reaction was clearly shown in the adaptation of this technology by the Overman group in their total synthesis of asperazine (Schemes 1.5-1.6).[5d] They rapidly constructed ynoate **1.38** from D-serine and perform Pd-catalyzed hydrostannylation to provide vinyl stannane **1.39** to be used in a Stille coupling. The coupling partner was synthesized from L-tryptophan methyl ester hydrochloride by way of reduction to the indoline, Boc-protection, reduction of the ester to the corresponding primary alcohol, and then protection with 2,2-dimethoxypropane to give indoline **1.41**. Ortho-directed metalation with *sec*-BuLi followed by quenching with iodine and dehydrogenation with DDQ provided the Stille coupling partner **1.42**.



Scheme 1.4. Overman's Total Synthesis of (–)-Chimonanthine



Scheme 1.5. Overman's Synthesis of Asperazine Precursor **1.44**



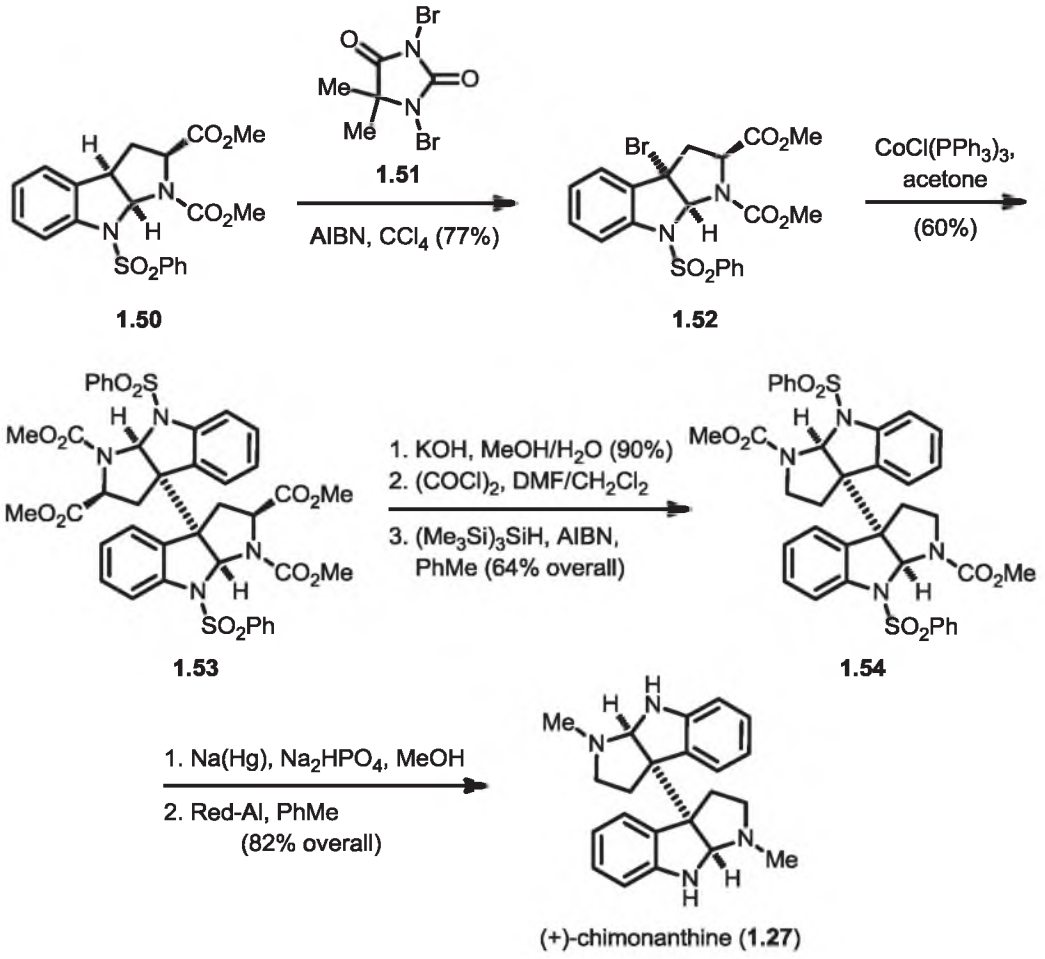
Scheme 1.6. Overman's Total Synthesis of Asperazine

After the Stille coupling between stannane **1.39** and iodide **1.42**, thermal deprotection of the indole-Boc protecting group gave indole **1.43**. Amide formation with *o*-iodoaniline and protection with SEMCl provided **1.44**. Finally, the crucial Heck reaction was performed followed by SEM removal and a substrate-controlled hydrogenation to provide advanced tryptophan dimer **1.46**.

Protecting group manipulation, diastereomer separation, and then reduction with lithium triethylborohydride followed by methanolysis gave pyrroloindoline **1.48** (Scheme 1.6). The primary alcohols were oxidized to the corresponding acids and coupled with D-phenylalanine to provide peptide **1.49**. After protecting group removal, diketopiperazine formation completed the synthesis of the natural product asperazine in 22 steps from D-serine.

Movassaghi's synthesis of (+)-chimonanthine involved the direct dimerization of C(3)-bromo pyrroloindoline **1.52** via the corresponding tertiary benzylic radical using a Co(I) reagent (Scheme 1.7).[6a] Barton radical bis-decarboxylation of **1.53** gave **1.54**, followed by reduction of the sulfonamide protecting groups and reduction of the carbomethoxy protecting groups giving the natural product in 10 steps from L-tryptophan methyl ester hydrochloride.

In addition to the synthesis of symmetrical pyrroloindoline dimers, the Movassaghi group has also developed a novel diazene fragmentation of pyrroloindoline heterodimers that readily accesses not only asymmetrical pyrroloindoline dimers but also a variety of C(3)-carbon substituted pyrroloindolines (Scheme 1.8). Substitution of the bromide in **1.55** with azide and reduction provided **1.56**.



Scheme 1.7. Movassaghi's Total Synthesis of (+)-Chimonanthine

After synthesis of the sulfamoyl chloride, addition of an appropriate amine provided sulfamide **1.57**. Subsequent oxidation with NCS initiated a sequence that involves SO_2 expulsion to form diazene **1.59** which may be isolated. The diazene was irradiated to expulse dinitrogen to form solvent caged radicals that then combine giving C(3)-carbon pyrroloindoline **1.60** (Scheme 1.8).

The Movassaghi group also developed Friedel-Crafts based technology starting from C(3)-bromo pyrroloindolines using halophile Ag(I) and a broad range of π-nucleophiles

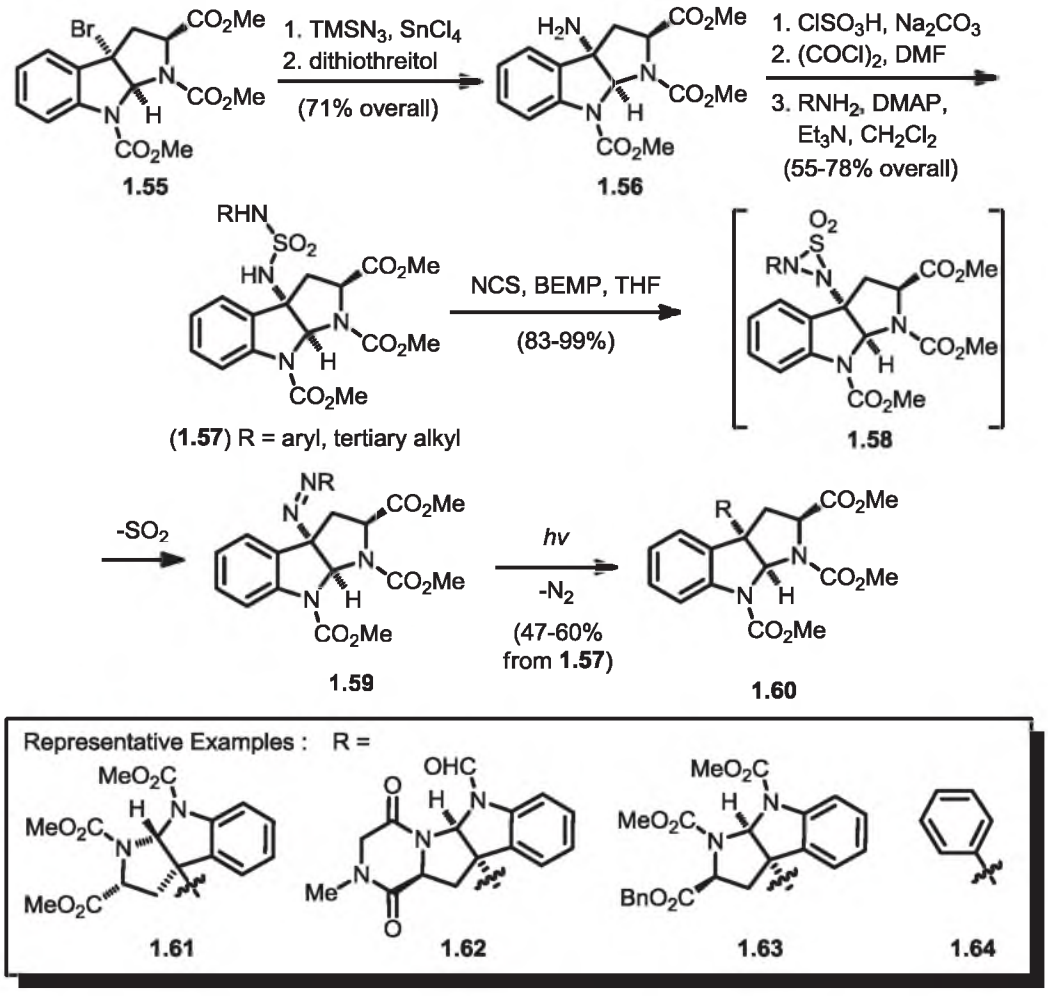
(Scheme 1.9). This reaction was then utilized to complete a total synthesis of (+)-naseseazine A (Scheme 1.10).

The synthesis of (+)-naseseazine A begins with Cbz protection and Horner-Wadsworth-Emmons olefination of indole **1.73**. Enantioselective hydrogenation followed by diketopiperazine synthesis provided indole **1.77**. Next, a Miyaura boration converted the aryl bromide to a boronate with subsequent conversion to the tetrafluoroborate salt **1.79**. Nucleophilic substitution of **1.79** on bromide **1.65** in the presence of Ag(I) and deprotection provided the natural product (+)-naseseazine A in 11 steps from indole **1.73** (Scheme 1.10).

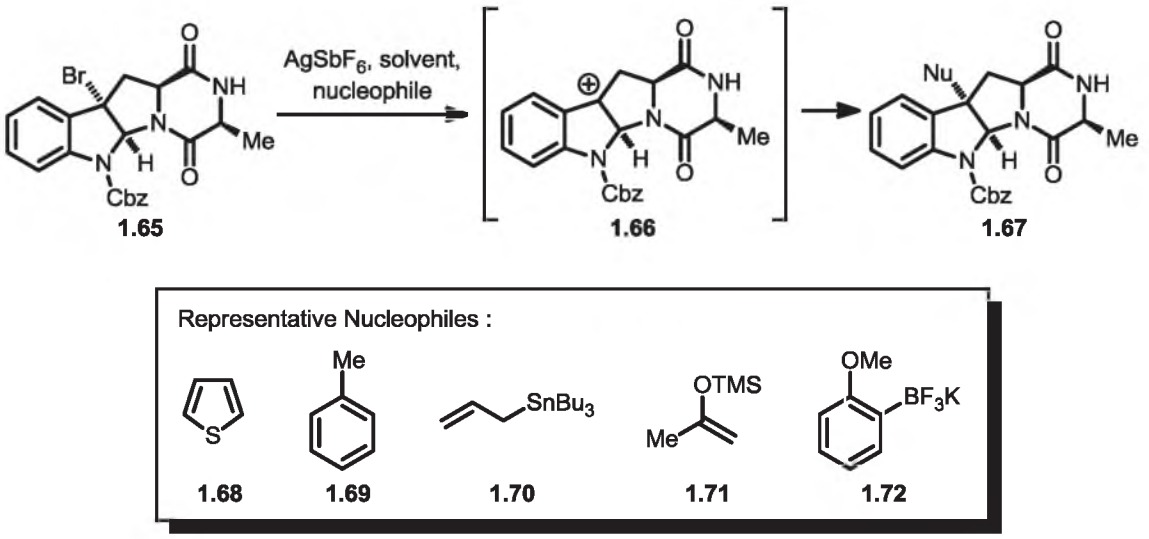
C(3)-Hydroxy Substituted Pyrroloindolines

Pyrroloindolines that are C(3)-hydroxy substituted are also found in nature and many synthetic methods have been developed in order to construct this bond.[7] A representative array of this class of compounds is given in Figure 1.2.[8] Worthwhile mentions in total synthesis include Corey's synthesis of okaramine N and Danishefsky's synthesis of himastatin.[9,10]

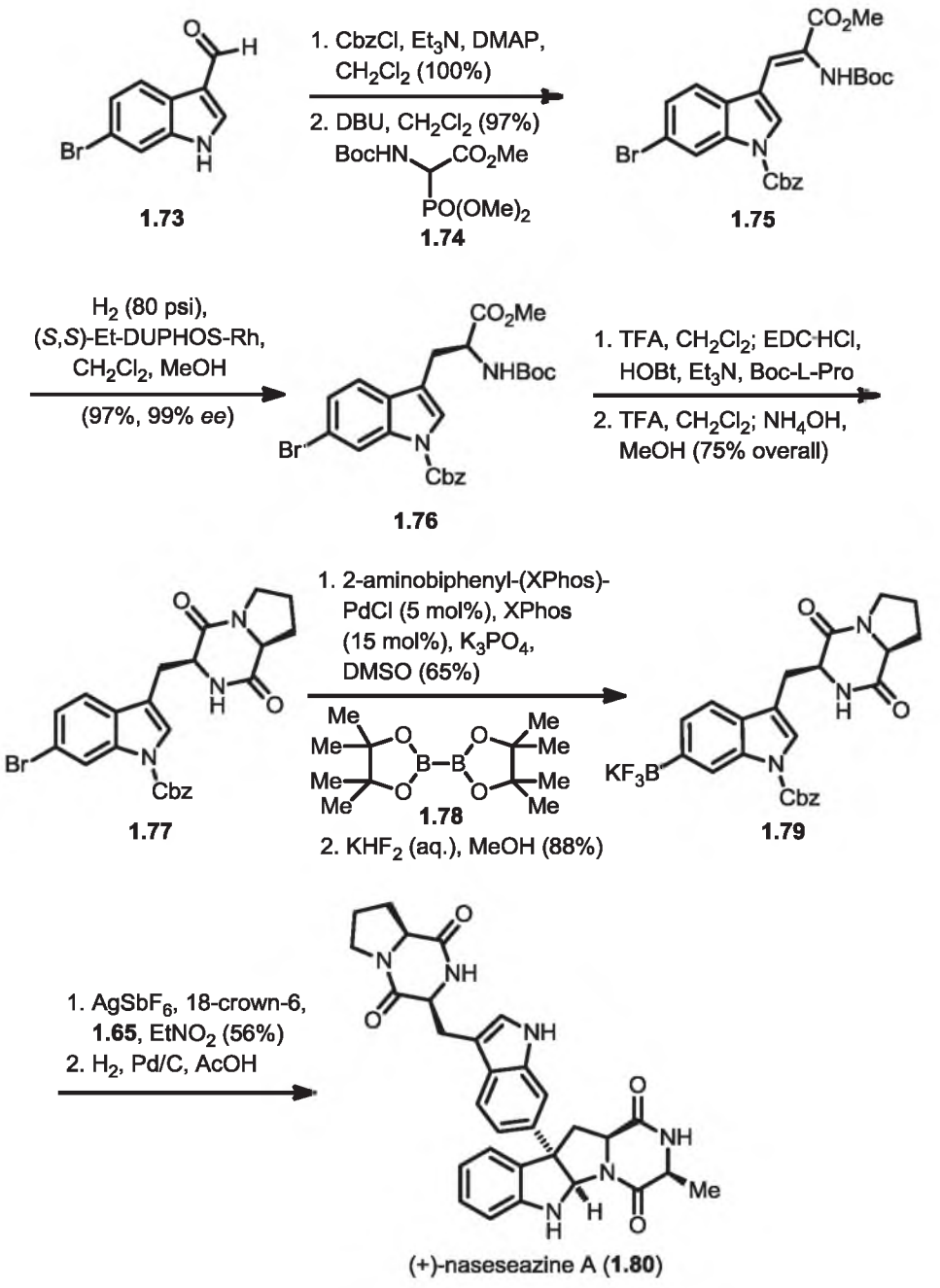
First, Corey developed interesting methodology for the synthesis of okaramine N that involved a palladium catalyzed indolocyclization, the development of a novel protecting group for the indole-[2,3]-π bond, and selective photooxygenation (Scheme 1.11).[9] The synthesis began with the reductive alkylation of amine **1.86** with aldehyde **1.87** to give tryptophan **1.88**. Boc protected tryptophan was then reduced to a mixture of indolines **1.89** and **1.90** and this mixture underwent nucleophilic substitution with propargyl acetate **1.91**. Dehydrogenation of the indoline and hydrogenation of the alkyne to the



Scheme 1.8. Movassaghi's Diazene Fragmentation Technology



Scheme 1.9. Movassaghi's Friedel-Crafts Based Technology



Scheme 1.10. Movassaghi's Total Synthesis of (+)-Naseseazine A

alkene provided tryptophan **1.92**. Hydrolysis of the ester followed by replacement of the Boc group with Fmoc then gave tryptophan **1.93** and coupling with **1.88** gave bis-tryptophan **1.94**.

Palladium promoted indolocyclization and Fmoc removal generated octacyclic diketopiperazine **1.95**. Corey next introduced a novel indole-[2,3]-π bond protecting group, MTAD, through a reversible ene reaction. Photooxygenation then cyclized the unprotected indole and thermolysis of the protecting group provided the natural product okaramine N in 13 steps overall.

Danishefsky's synthesis of himastatin was also a landmark synthesis of a C(3)-hydroxy pyrroloindoline natural product.[10a-c] The synthesis included electrophilic oxygenation of the indole-[2,3]-π bond and complex cyclic peptide synthesis (Schemes 1.12-1.15).

The synthesis began with the conversion of commercially available tosylate **1.98** to bromide **1.99** through methanolysis and epoxide formation followed by opening the epoxide with LiBr and TBS protection afforded bromide **1.99**. Formation of the enolate and trapping with DBAD and cyclization gave a mixture of piperazic esters **1.100** and **1.101**. The desired isomer was Boc deprotected and protection with Teoc followed by hydrolysis gave piperazic acid **1.103**. The undesired isomer **1.100** can also be converted to **1.103** by using an epimerization strategy (Scheme 1.12).

With the piperazic acid in hand, they then focused on the synthesis of pentadepsipeptide **1.109** (Scheme 1.13). The allyl ester of D-threonine was prepared and the hydroxy group protected as a silyl ether. Peptide coupling with Fmoc protected leucine and removal of the Fmoc group gave dipetide **1.106**. Subsequent coupling with

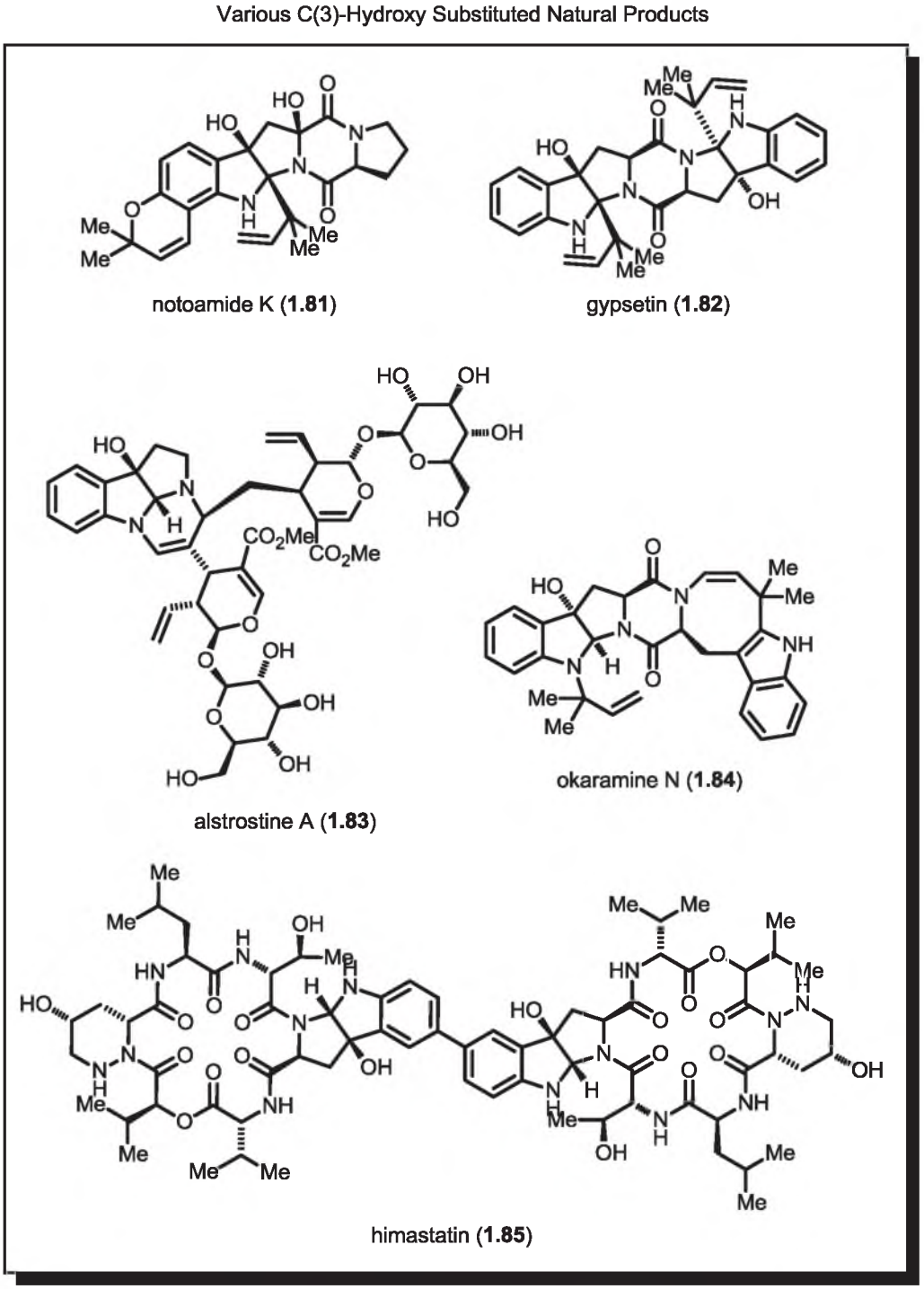
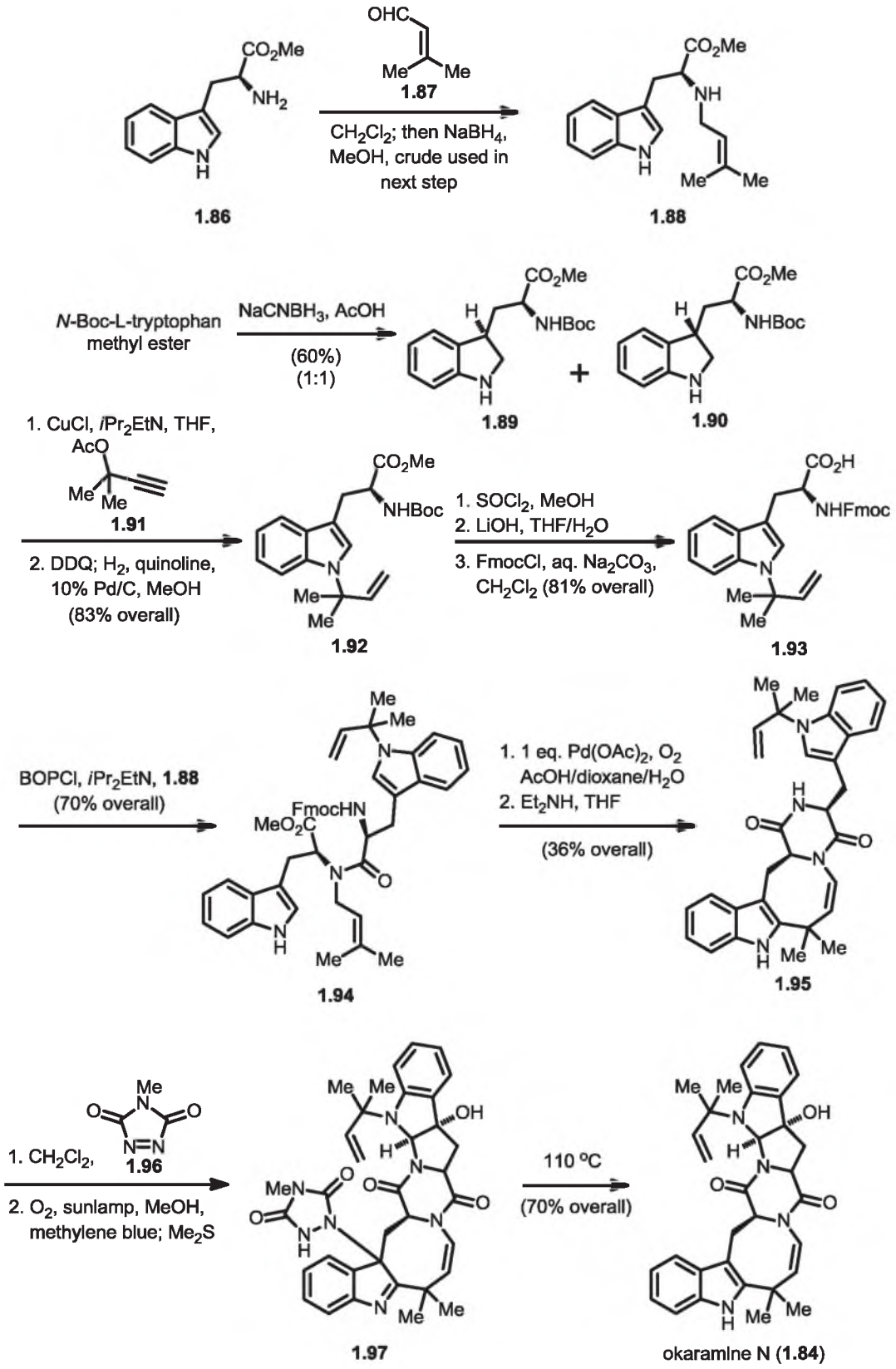
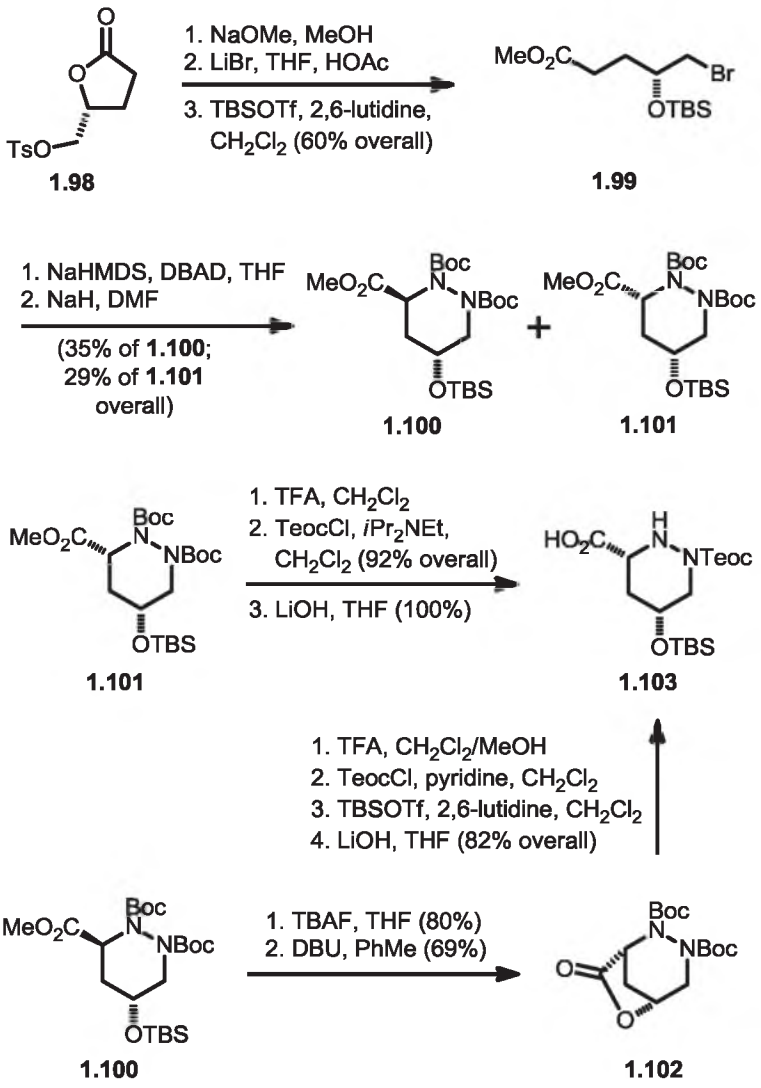


Figure 1.2. Representative C(3)-Hydroxy Pyrroloindolines



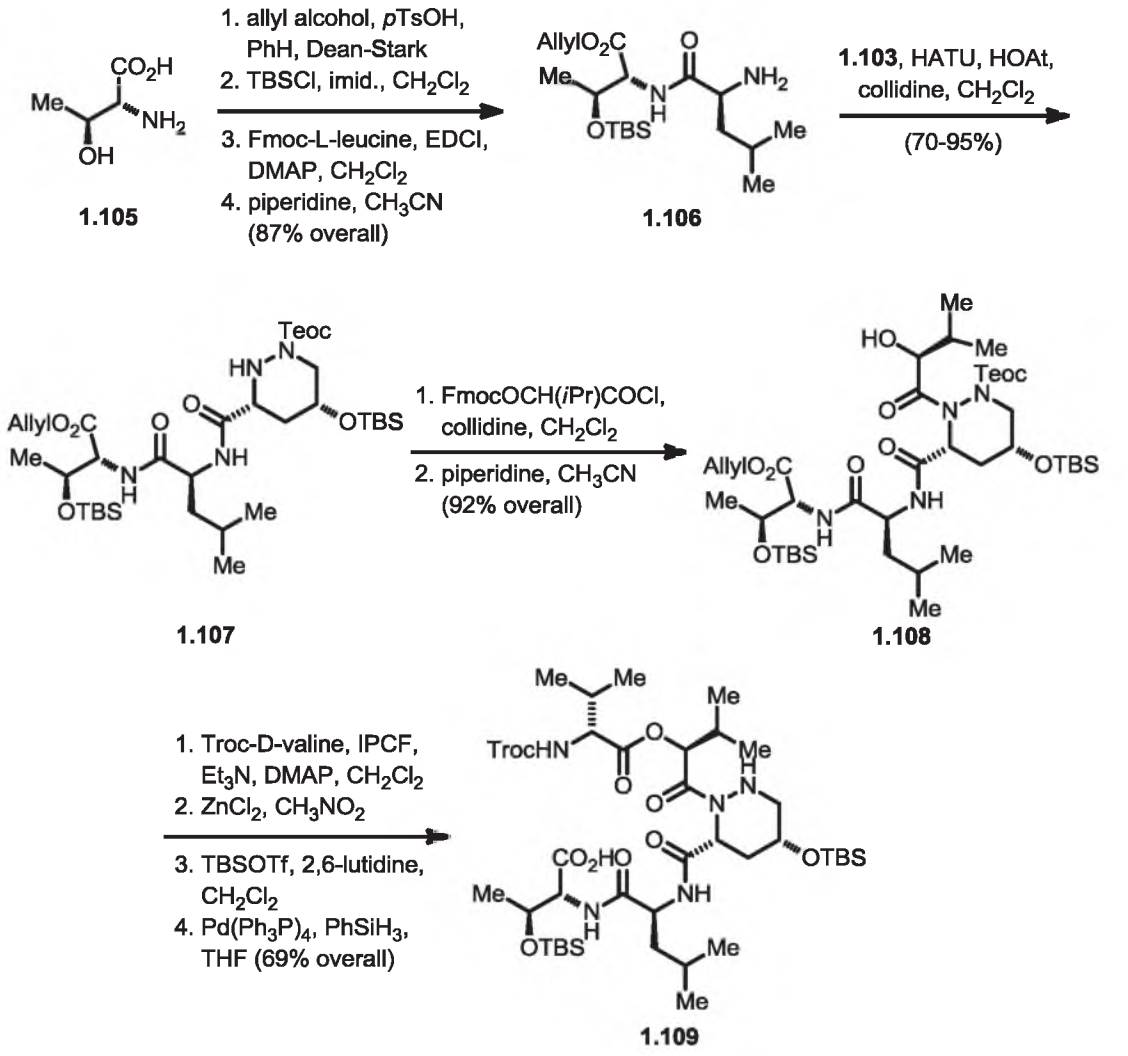
Scheme 1.11. Corey's Total Synthesis of Okaramine N



Scheme 1.12. Danishefsky's Synthesis of Piperazic Acid **1.103**

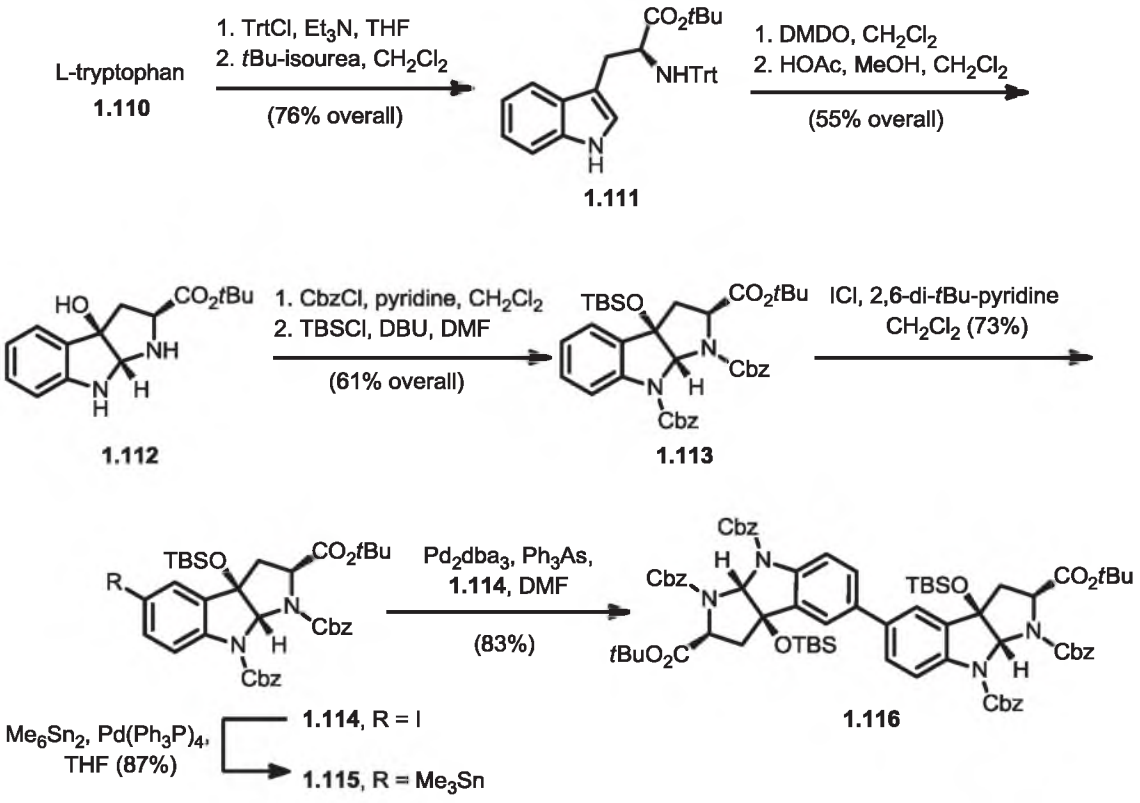
piperazic acid **1.103** afforded tripeptide **1.107**. Coupling with a hydroxy valeric acid derivative, deprotection, another coupling with a D-valine derivative and deprotection yielded the desired acid **1.109** (Scheme 1.13).

The Danishefsky group then completed the total synthesis by performing an oxycyclization on tryptophan **1.111** using DMDO to provide the C(3)-hydroxy pyrroloindoline **1.112** (Scheme 1.14). After protecting group introduction, the aryl

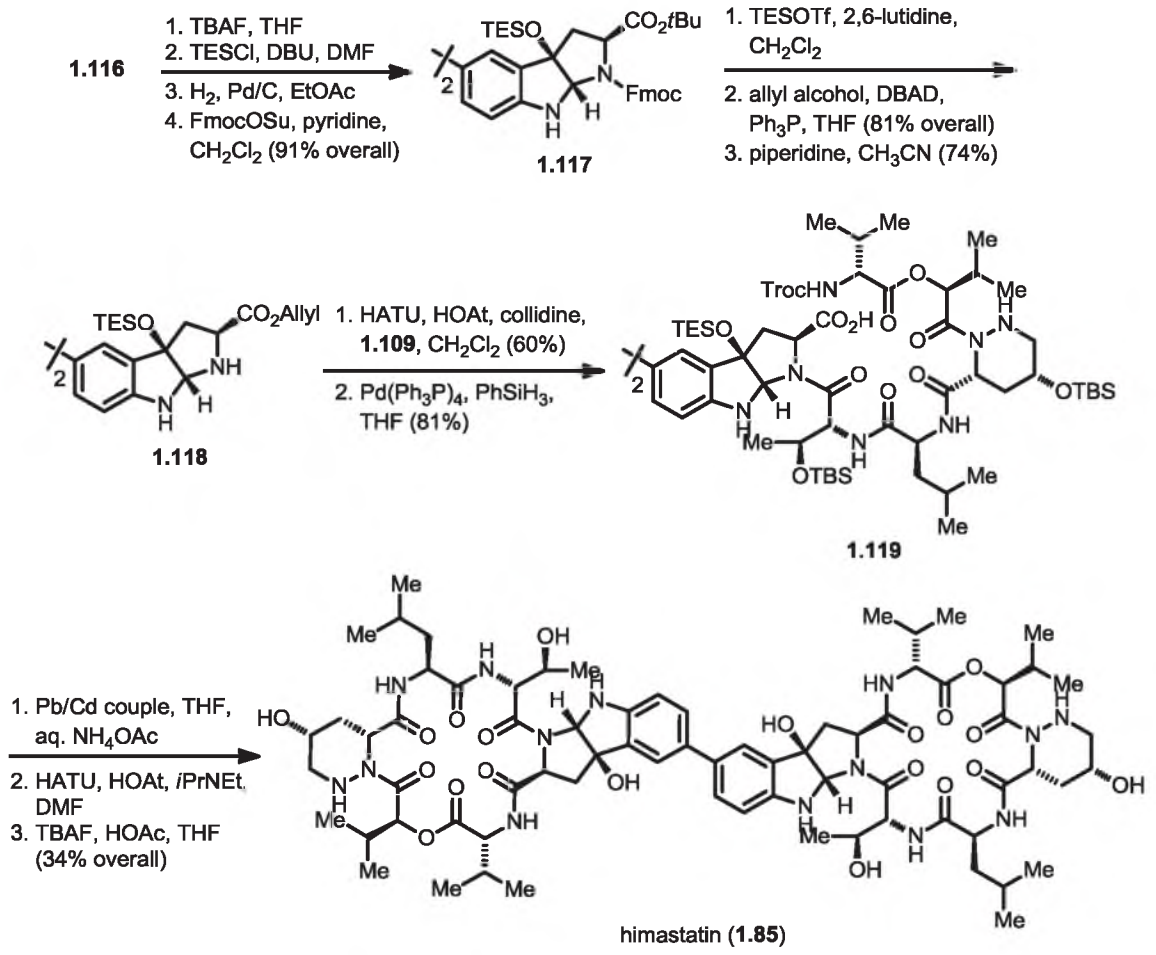


Scheme 1.13. Danishefsky's Synthesis of Pentadepsipeptide **1.109**

nucleus was halogenated with ICl and half of the resulting aryl iodide was converted into the stannane **1.115** under Pd catalysis. A Stille coupling between aryl iodide **1.114** and stannane **1.115** gave the pyrroloindoline dimer **1.116**. Protecting group manipulation followed by introduction of depsipeptide **1.109** and macrolactamization of the resulting peptide **1.119** generated the natural product himastatin in 32 steps for the longest linear sequence (Scheme 1.15).



Scheme 1.14. Danishefsky's Synthesis of Dimer **1.116**



Scheme 1.15. Danishefsky's Total Synthesis of Himastatin

C(3)-Nitrogen Substituted Pyrroloindolines

Heterodimeric indolines that contain a C(3)-N(1′) bond represent a class of structurally unique molecules with interesting biological properties (Figure 1.3).[11] Our laboratory began research on the construction of the C(3)-N(1′) bond to fill a relatively large gap in the literature to construct such a bond. At the onset of our research only one synthetically useful method was known and had been developed by the Takayama group in their total synthesis of (±)-psychotrimine (Scheme 1.17).[12] This method has the

drawback in that the pyrroloindoline motif is synthesized over many steps.

Shortly thereafter, the Baran group published their technology for the formation of the C(3)-N(1′) bond which relied on the oxidative cyclization of tryptamine derivatives with electrophilic nitrogen and also focuses on the synthesis of (±)-psychotrimine (Scheme 1.16).[13] This cyclization is believed to be mechanistically similar to that of the cyclization of tryptamine derivatives with electrophilic selenium as displayed in Danishefsky's syntheses of amauromine and ardeemin. It involved in situ activation of aniline **1.125** to form *N*-iodoaniline **1.127** that acts as a source of electrophilic nitrogen and interacts with the indole-[2,3]-π double bond as in **1.128**.

The Takayama synthesis of psychotrimine began with a Strecker reaction between indoline and 2-bromobenzaldehyde to give **1.131** (Scheme 1.17). Alkylation of **1.131** with nitroethylene and dehydrogenation with DDQ provides indole **1.133** and the requisite C(3)-N(1′) bond. Reduction with Fe powder and Boc protection generated amidine **1.134**, followed by a Cu-catalyzed intramolecular Buchwald-Hartwig coupling and reduction gave pyrroloindoline **1.136** as a racemic mixture in the *cis* configuration. The aniline nitrogen was Boc protected and ortho-metalation followed by quenching with iodine provides indole **1.137**. Tryptamine synthesis by reacting the indole with nitroethylene, reduction of the nitro group to a free amine with Fe powder followed by protection of the amine with *p*-nitrobenzenesulfonyl chloride gave a sulfonamide. Methylation of the sulfonamide with dimethylsulfate and base, and deprotection of the Boc group gave **1.139**. Cu-catalyzed Buchwald-Hartwig amination of aryl iodide **1.139** with tryptamine **1.140** and nosyl group deprotection afforded (±)-psychotrimine in 16 steps.

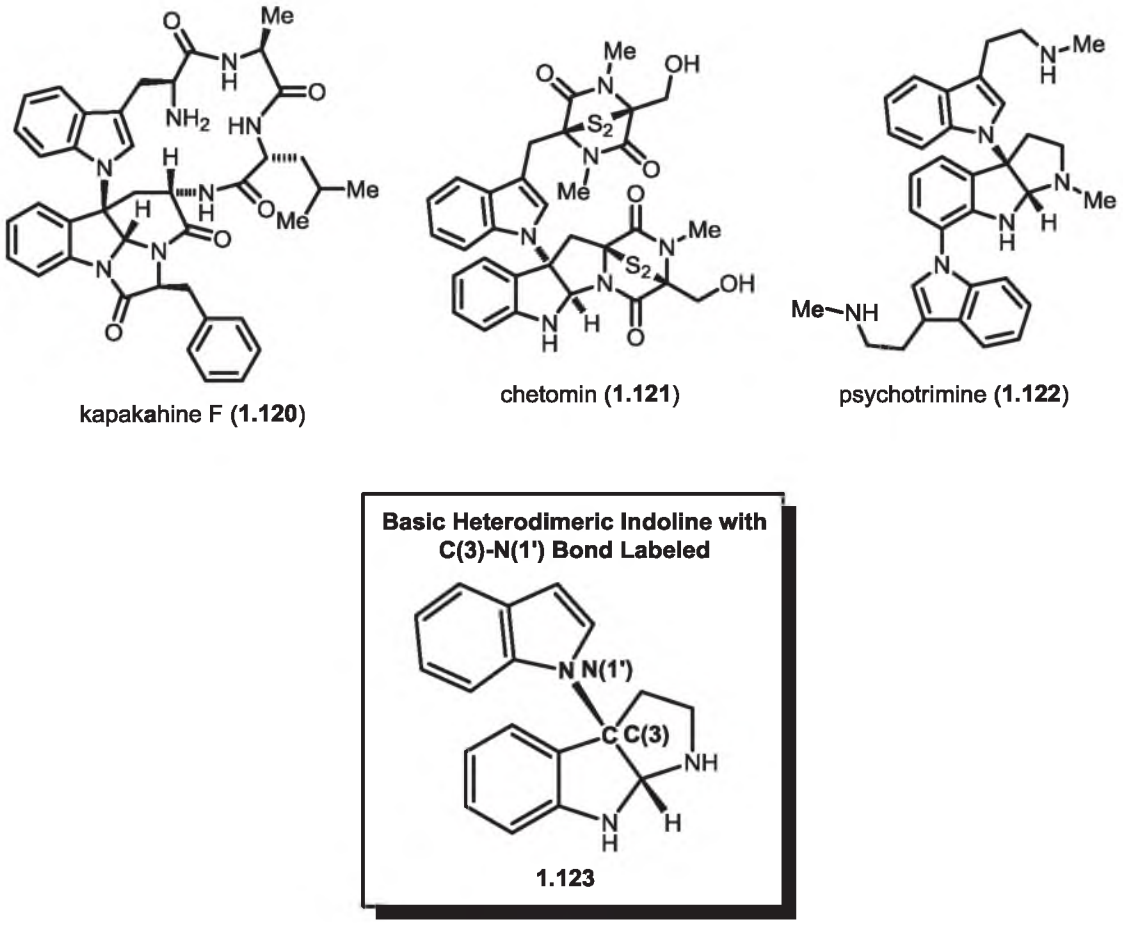
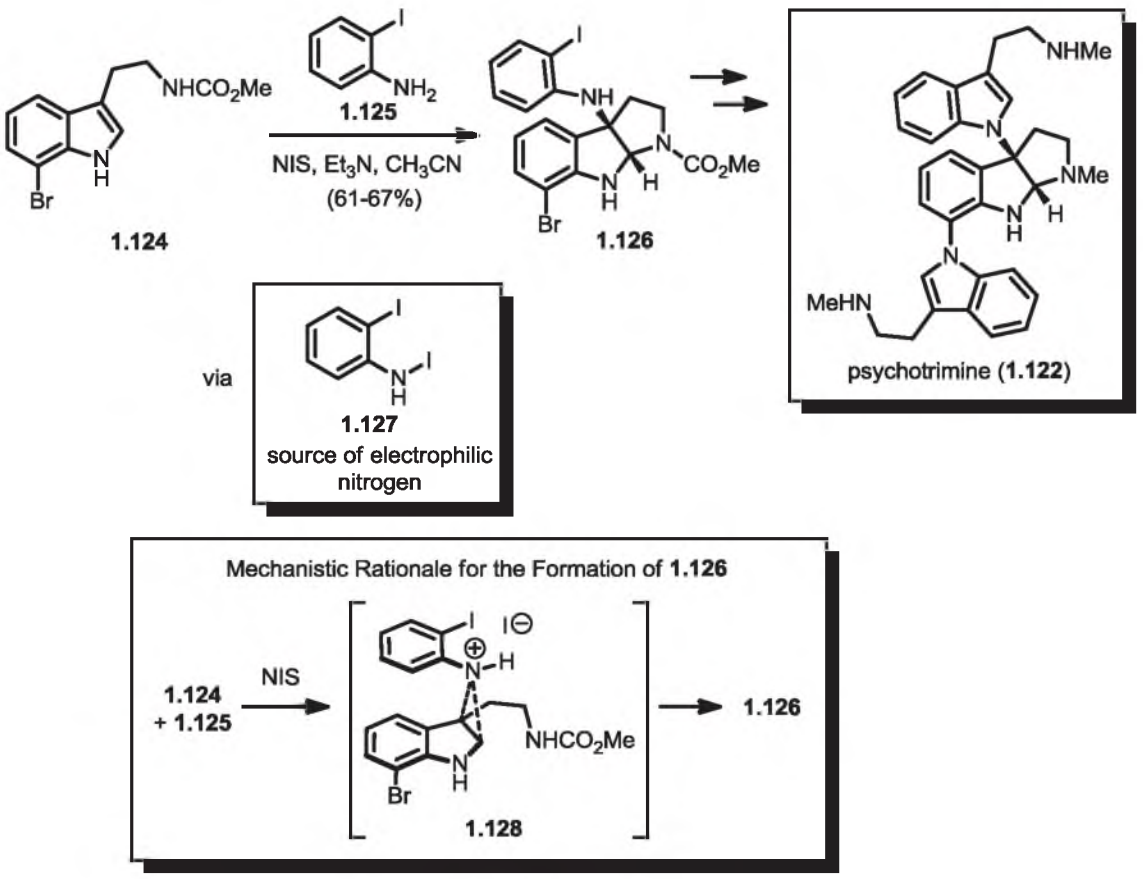
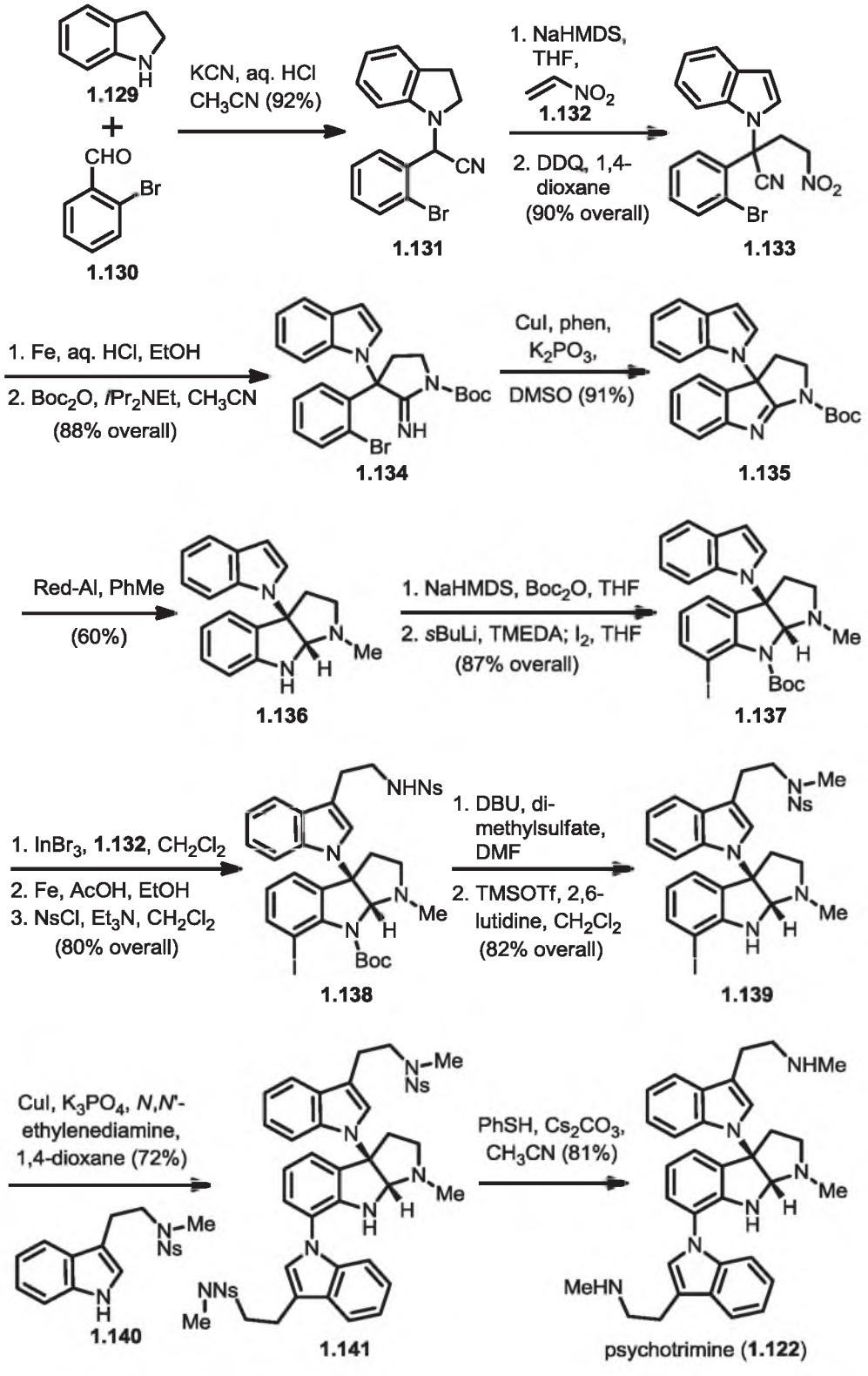


Figure 1.3. Representative C(3)-Nitrogen Pyrroloindolines



Scheme 1.16. Baran's C(3)-N(1′) Bond Forming Technology



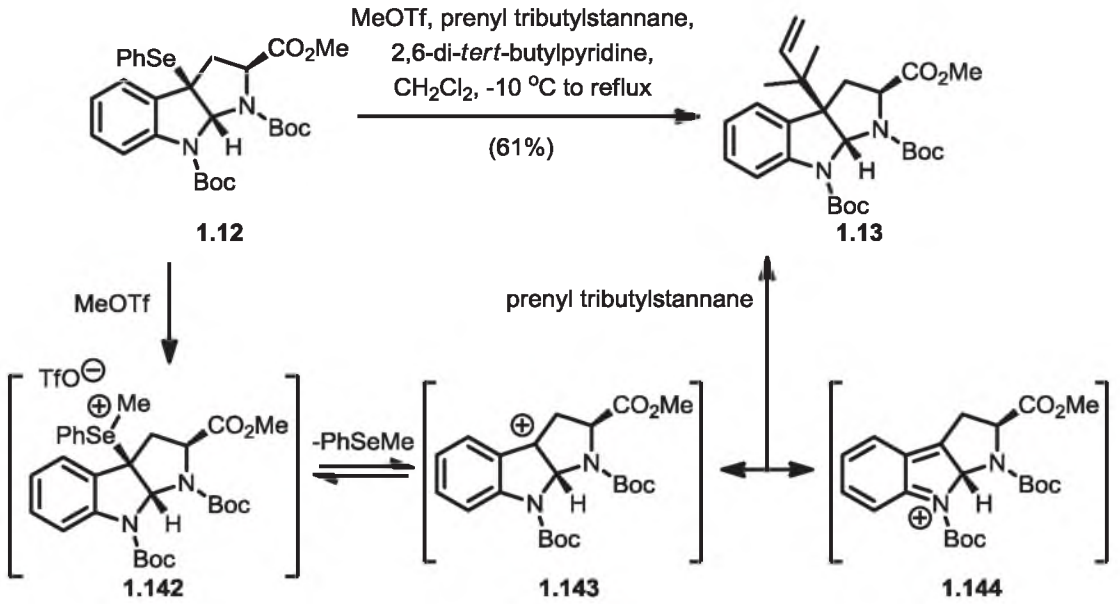
Scheme 1.17. Takayama's Total Synthesis of (±)-Psychotrimine

Our Approach Toward C(3)-N(1′) Heterodimeric Indolines

Our laboratory initially focused on utilizing C(3)-halogen substituted pyrroloindolines as precursors to C(3)-N(1′) heterodimeric indolines by the direct nucleophilic substitution of the halogen with indole.[14] The primary inspiration for this approach came from the pioneering work by Danishefsky and coworkers on the substitution of C(3)-phenylseleno pyrroloindolines (Scheme 1.18).[4] They reported that the activation of phenylseleno pyrroloindoline **1.12** with MeOTf presumably forms the cationic selenium intermediate **1.142** that acts as a leaving group to generate a stabilized carbocation (**1.143** and **1.144**) that is then trapped by prenyl tributylstannane to give pyrroloindoline **1.13** (Scheme 1.18).

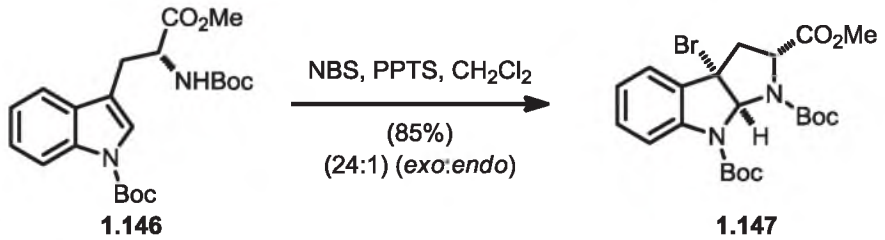
Our laboratory wished to use this process as a template to form the proposed benzylic carbocationic intermediate **1.143** and trap this intermediate with an *N*-metalated-indole nucleophile. It was hypothesized that a C(3)-halogen or C(3)-triflate substituent would serve as alternative sources of carbocation **1.143** due to their perceived similar ability to readily ionize (Scheme 1.19).

It was established by de Lera and coworkers that C(3)-bromo pyrroloindolines could be synthesized from (D)-tryptophan in high diastereoselectivity analogous to the methodology developed by Danishefsky and coworkers in their synthesis of C(3)-phenylseleno pyrroloindoline **1.12** (Scheme 1.20).[15] Given the ready availability of bromopyrroloindoline **1.147** as essentially a single diastereomer from bis-Boc tryptophan **1.146**, we decided to utilize it as a source of carbocation **1.143** and attempt to couple it with an *N*-metalated-indole.



Scheme 1.18. Danishefsky's Substitution of C(3)-Phenylseleno Pyrroloindolines

Scheme 1.19. Alternative Sources of Carbocation **1.143**

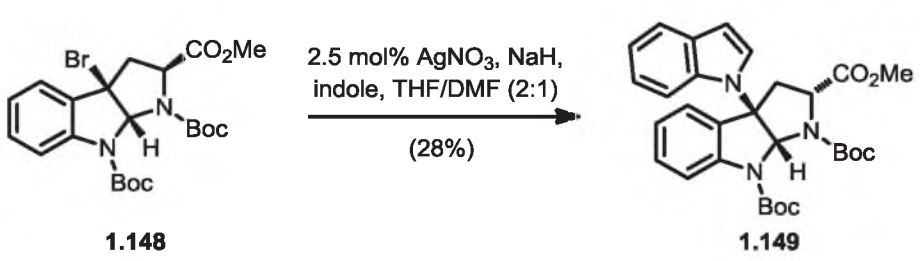


Scheme 1.20. De Lera's Synthesis of C(3)-Bromo Pyrroloindoline **1.147**

A model reaction was designed that utilized bromopyrroloindoline **1.148** and the sodium salt of indole (Scheme 1.21). Silver nitrate was added to the reaction mixture due to the well known ability of Ag(I) salts to activate organic halides in substitution reactions with nucleophiles. In the event, the reaction proceeded upon addition of **1.148** to a mixture of *N*-sodio-indole and $AgNO_3$ to give heterodimer **1.149** in 28% yield as a single diastereomer (Scheme 1.21). Interestingly, the methyl ester had epimerized from the *exo* isomer (*syn-cis*) to the thermodynamically more stable *endo* isomer (*anti-cis*) under the strong base conditions used in the substitution reaction.[2a]

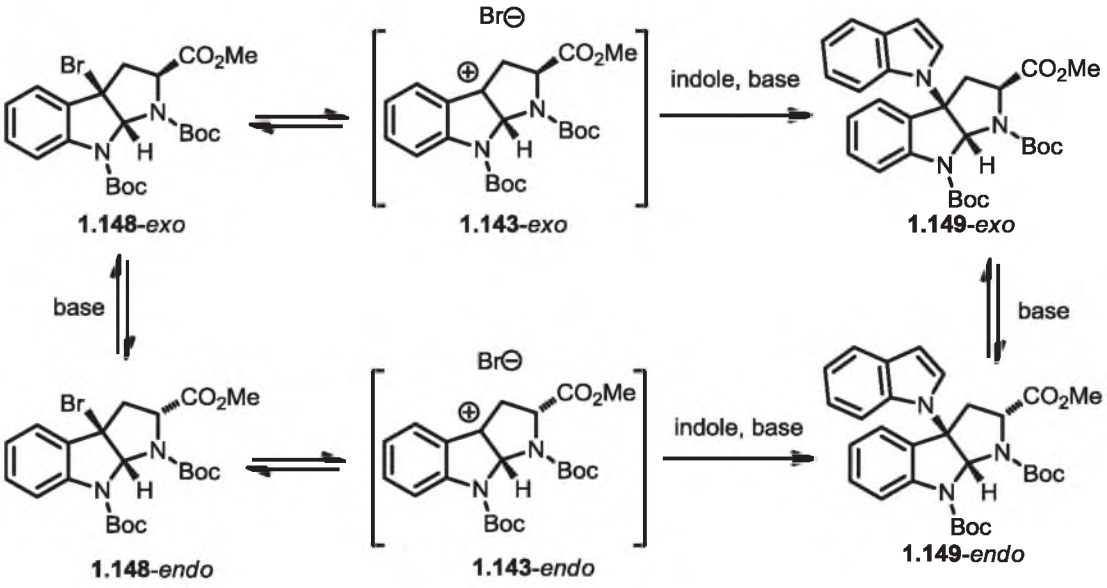
We initially proposed that the mechanism for the heterodimerization involved production of carbocation **1.143** followed by trapping with *N*-metalated-indole in an S_N1 fashion (Scheme 1.22). The reaction was optimized using indole as the standard nucleophile and it was found that superior yields were achieved when a solution of potassium *tert*-butoxide in THF was added slowly to a mixture of indole and an excess of **1.148** in acetonitrile (Table 1.1). Under these conditions, a mixture of *endo*:*exo* isomers were generally obtained due to thermodynamic equilibration with potassium *tert*-butoxide with a preference of the *endo* isomer over the *exo* isomer.

An initial investigation of the scope of the reaction was also performed and it was found that a variety of substituted indoles were valid substrates for the reaction (Table 1.1). Protected tryptamine analogues could be used, but low yields were observed when the substrate contained groups sensitive to the reaction conditions (entries 12 and 13, Table 1.1).



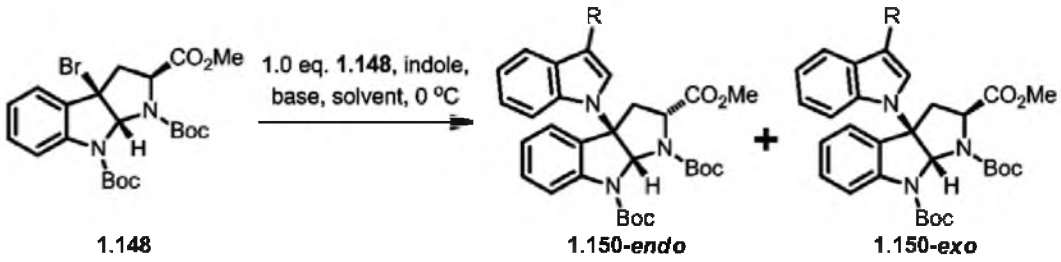
1.148 1.149

Scheme 1.21. Synthesis of Heterodimer **1.149**

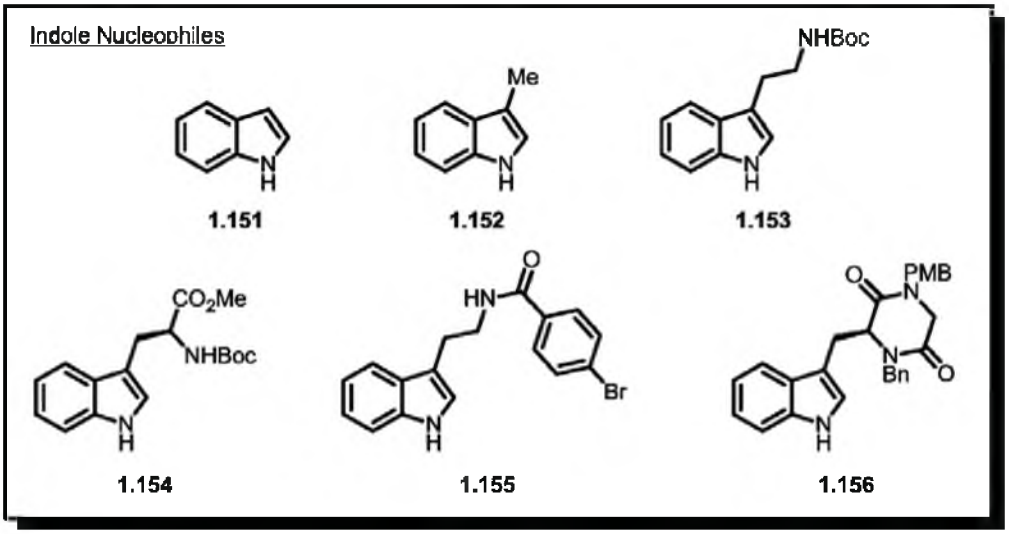


Scheme 1.22. Initial Mechanistic Proposal for the Production of **1.149**

Table 1.1. Optimization and Scope of Heterodimerization



1.148 **1.150-*endo*** **1.150-*exo***

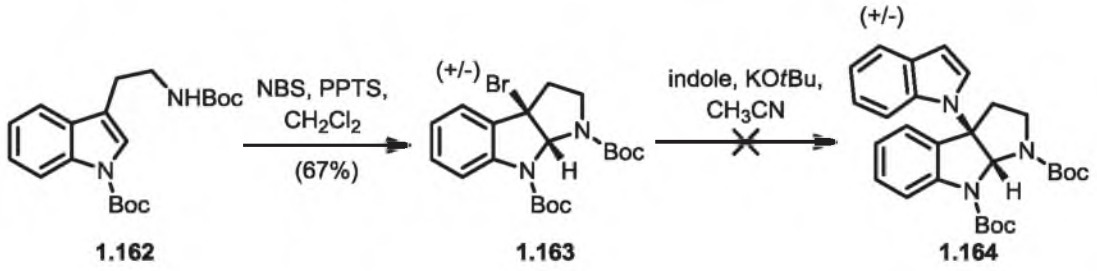


entry	indole (eq)	base (eq)	solvent	dimer (*endo:exo*)[3]	yield (%)
1	**1.151** (1.2)	NaH (1.1)[1]	THF:DMF (2:1)	**1.149** (>95:5)	28
2	**1.151 (2.0)**	**NaH (1.75)**	**HMPA[2]**	**1.149 (3:1)**	**63**
3	**1.151** (1.5)	KO*t*Bu (1.2)	CH_3CN	**1.149** (13:1)	43
4	**1.151 (1.5)**	**KO*t*Bu (1.2)**	**CH_3CN[2]**	**1.149 (5:1)**	**47**
5	**1.152** (1.5)	NaH (1.4)	DMF:HMPA (5:1)[2]	**1.157** (4:1)	59
6	**1.152 (1.5)**	**KO*t*Bu (1.2)**	**CH_3CN**	**1.157 (11:1)**	**43**
7	**1.153** (1.3)	KO*t*Bu (2.0)	CH_3CN	**1.158** (>95:5)	26
8	**1.151 (0.7)**	**KO*t*Bu (2.0)**	**CH_3CN**	**1.149 (7:1)**	**82**
9	**1.151** (0.7)	KO*t*Bu (2.0)	CH_3CN	**1.149** (5:1)	79
10	**1.151 (0.7)**	**KO*t*Bu (1.5)**	**CH_3CN**	**1.149 (10:1)**	**64**
11	**1.152**(0.7)	KO*t*Bu (2.0)	CH_3CN	**1.157** (3:1)	81
12	**1.153 (0.7)**	**KO*t*Bu (2.0)**	**CH_3CN**	**1.158 (>95:5)**	**48**
13	**1.154** (0.7)	KO*t*Bu (2.0)	CH_3CN	**1.159** (>95:5)	38
14	**1.155 (0.7)**	**KO*t*Bu (2.0)**	**CH_3CN**	**1.160 (>95:5)**	**78**
15	**1.156** (0.7)	KO*t*Bu (2.0)	CH_3CN	**1.161** (5:1)	76

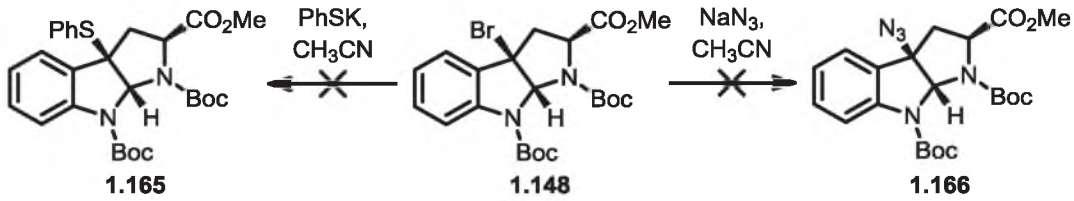
[1]: $AgNO_3$ (2.5 mol%) was used as an additive

[2]: Reaction mixture was allowed to warm to room temperature

[3]: Ratio determined using ^1H NMR



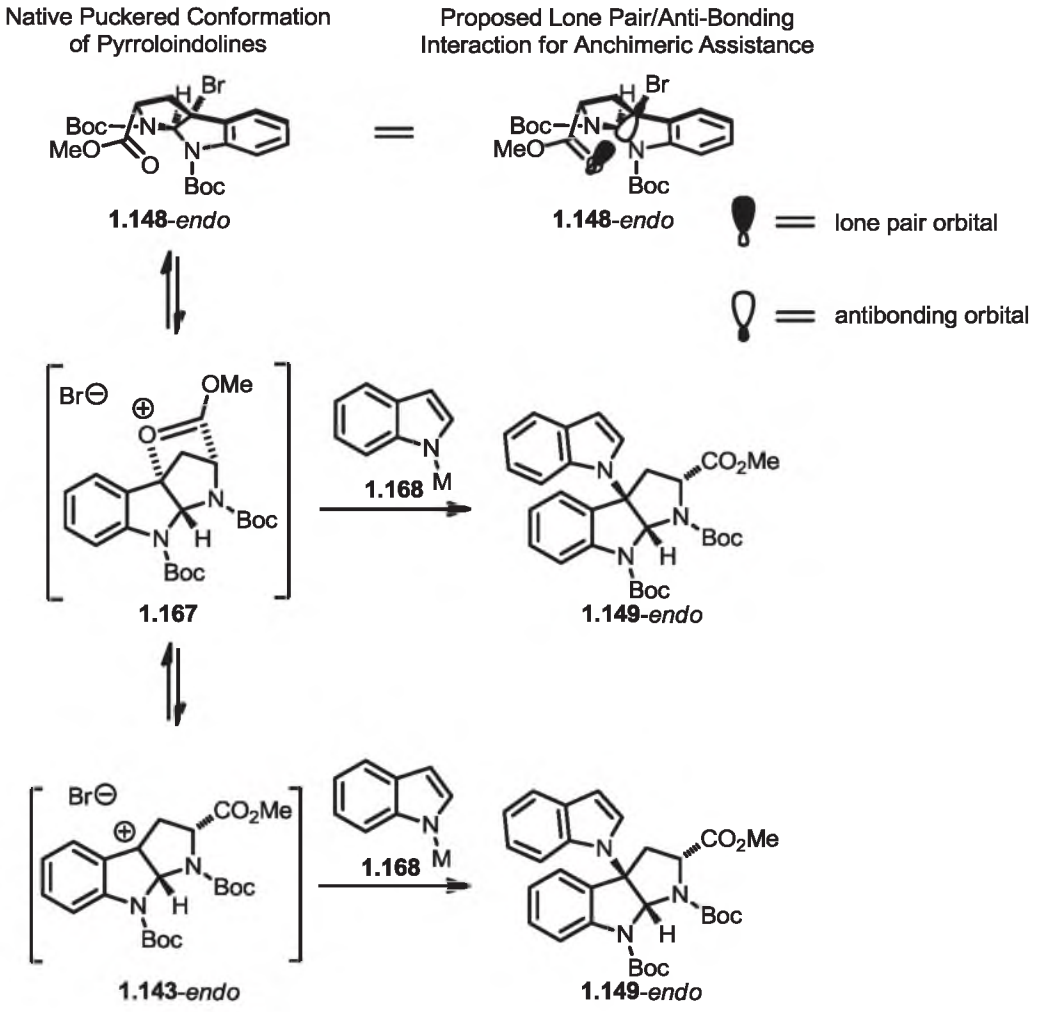
Scheme 1.23. Attempted Synthesis of Heterodimer **1.164**



Scheme 1.24. Attempted Coupling of **1.148** with Strong Nucleophiles

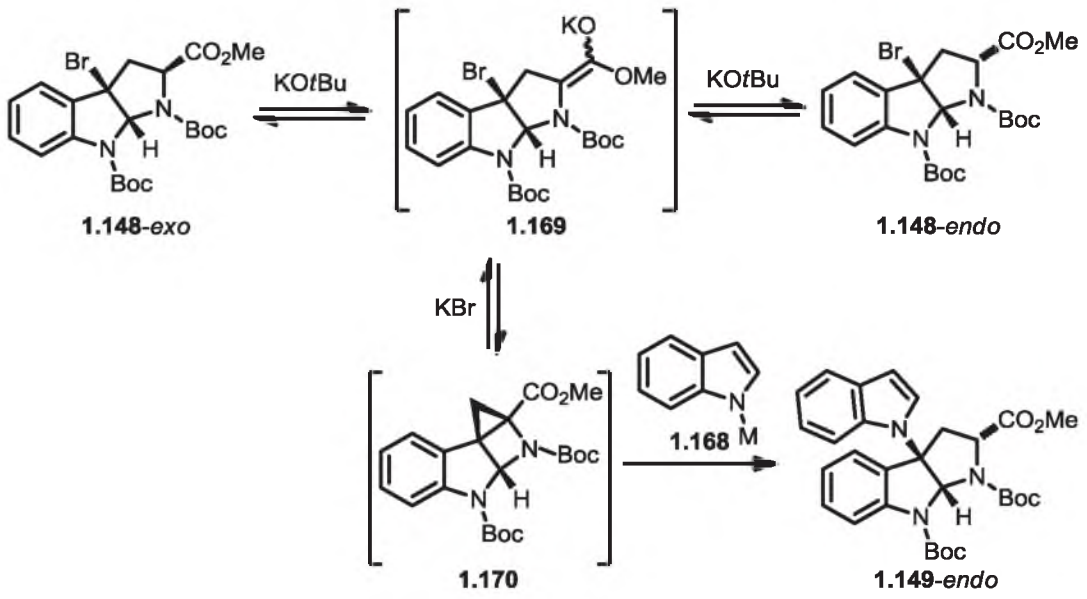
We were forced to reevaluate the proposed mechanism upon the attempted coupling between bromopyrroloindoline **1.163** and indole (Scheme 1.23). It became apparent that the ester was intimately involved in the mechanism and was necessary for the success of the reaction. Interestingly, we did not observe any coupled products from the reaction between bromopyrroloindoline **1.148** and NaN_3 or PhSK (Scheme 1.24).

This result led us to propose that since the coupling of **1.148** with nucleophiles only seemed to take place under conditions that affected the epimerization of the methyl ester, it was probable that the reactive isomer of **1.148** was the *endo* isomer rather than the *exo* isomer. It was believed that the *endo* methyl ester was set up to provide anchimeric assistance by way of the lone pair on the carbonyl oxygen in order to facilitate ionization of the bromide (Scheme 1.25).[16]



Scheme 1.25. Proposed Anchimeric Assistance Mechanism

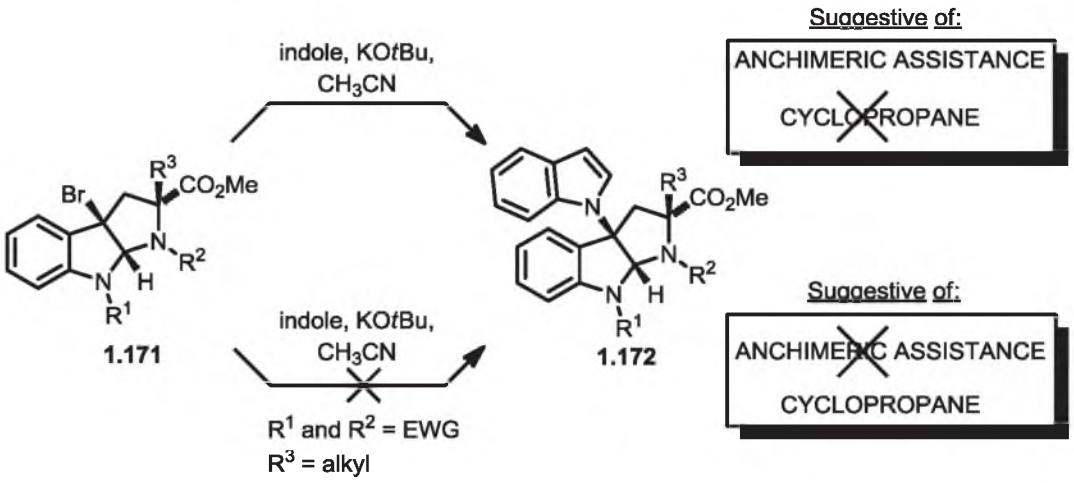
During this time, another appealing mechanism was devised that also explained the nonreactivity of **1.148** toward nucleophiles under conditions that were insufficiently basic enough to cause deprotonation of the methyl ester. This alternative mechanistic proposal involved the generation of the strained transient cyclopropane **1.170** from the enolate **1.169** (Scheme 1.26). In addition, precedent for the synthesis of cyclopropanes using an anionic ring closure has been documented.[14] The ring strain inherent in the cyclopropane would be alleviated by the addition of nucleophiles in an S_N2 reaction to



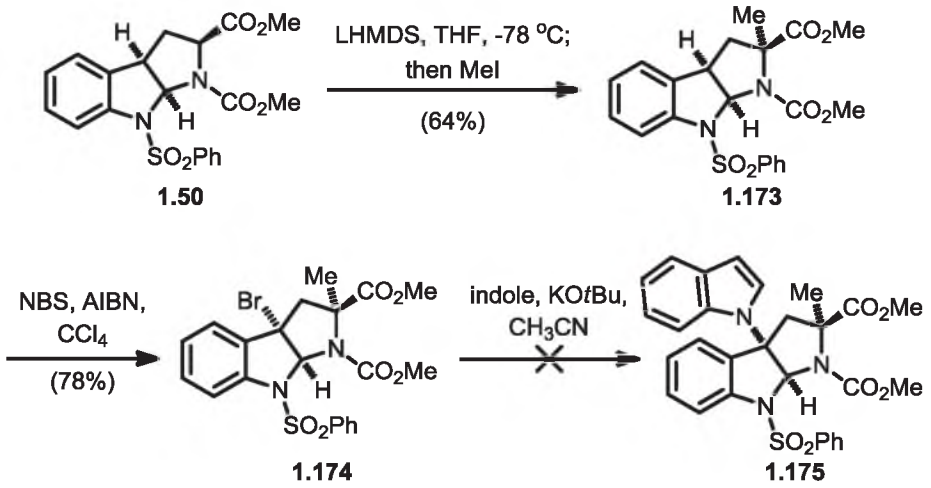
Scheme 1.26. Proposed Strained Cyclopropane Mechanism

give the enolate of the methyl ester. Kinetic protonation of the enolate would then lead to the *endo* isomer and equilibration under the reaction conditions would lead to the *exo* isomer.

A defining experiment was performed in order to differentiate between the two mechanisms. We hypothesized that the use of a bromopyrroloindoline that contained a non-enolizable ester that was fixed in the *endo* position, would supply valuable information. In this case, a successful reaction would disprove the cyclopropane mechanism while providing excellent support for the anchimeric assistance mechanism. Failure of the reaction would provide strong evidence against the anchimeric assistance mechanism (Scheme 1.27). To test this hypothesis, bromopyrroloindoline **1.174** was synthesized according to methodology developed by David Crich and coworkers (Scheme 1.28).[2a]



Scheme 1.27. Mechanistic Analysis of **1.171** to **1.172**



Scheme 1.28. Synthesis of **1.174** and Attempted Heterodimerization

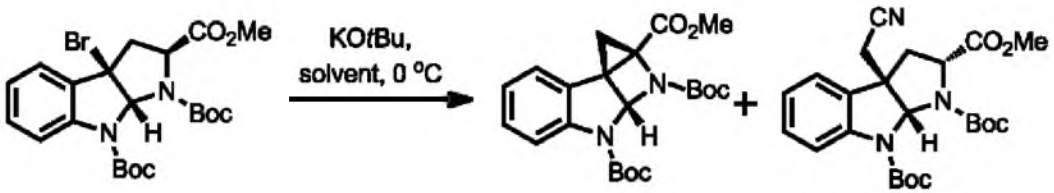
The known pyrroloindoline **1.50** was methylated using LHMDS and MeI to give **1.173** followed by radical bromination with NBS to provide **1.174**. Subjection of **1.174** to standard heterodimerization conditions only resulted in recovered starting material along with some decomposition. Given this result, we were led to believe that the cyclopropane mechanism was operative barring further experiments to the contrary.

Cyclopropylazetoindoline

We proposed that the bromopyrroloindoline **1.148** was decomposing during the heterodimerization reaction due to the fact that **1.148** was completely consumed during the reaction but that an excess of **1.148** was necessary for high yields (Table 1.1). In an effort to try to understand the decomposition pathway of **1.148** during the heterodimerization reaction, we performed a control reaction in the absence of a nucleophile. To our delight, when **1.148** was subjected to KO*t*Bu in CH_3CN we isolated cyclopropane **1.170** (cyclopropylazetoindoline) along with acetonitrile adduct **1.176** and starting material (Table 1.2).

During the optimization process for the generation of **1.170**, we found that as the amount of KO*t*Bu was increased the amount of adduct **1.176** was also increased at the expense of **1.170** (entries 2-4, Table 1.2). By switching the solvent to THF we were able to eliminate the formation of **1.176** while cleanly converting **1.148** to **1.170** in high yield in gram quantities (entry 5, Table 1.2). Also to our surprise was the stability of **1.170** in that it could be subjected to silica gel column chromatography, could be refluxed in THF for several hours, and could be stored at 0 °C for several weeks without noticeable decomposition. Additionally, we were hopeful that **1.170** could be used as an electrophile

Table 1.2. Isolation of Cyclopropylazetoindoline **1.170** and Optimization



1.148 **1.170** **1.176**

entry	KO*t*Bu (eq)	solvent	yield of 1.170[1]	1.170:1.176:1.148[2]
1	1.0	CH_3CN	44 %	1:0:1
2	**1.2**	**CH_3CN**	**55 %**	**11:3:5**
3	1.5	CH_3CN	20 %	1:2:1
4	**2.0**	**CH_3CN**	**0 %**	**0:1:0[3]**
5	*1.2*	*THF*	*89-95 %*	1:0:0

[1]: Isolated Yield

[2]: Ratio determined using ^{1}H NMR

[3]: 1.176 was isolated in 42% yield

due to the apparent addition of the anion of CH_3CN to **1.170** to form **1.176**. The geometry of cyclopropane **1.170** was optimized using density functional theory (DFT) calculations (Figure 1.4, coordinates given in Table 1.4).

The calculated carbon-carbon bond lengths about the cyclopropane in **1.170** for C(11)-C(17), C(15)-C(17), and C(11)-C(15) are 1.48 Å, 1.51 Å, and 1.57 Å, respectively (carbon numbering used is in Figure 1.4), and the carbon-carbon bond length for parent cyclopropane is 1.51 Å.[17] Given that the C(11)-C(15) bond is calculated to be an abnormally long 1.57 Å, in addition to the "push-pull" nature of the cyclopropane (refer to **1.182**), we can predict that the C(11)-C(15) bond would be the weakest bond and would undergo fragmentation when exposed to nucleophiles. While we have postulated that the reaction likely proceeds through an S_N2 addition of nucleophile, S_N2 additions of

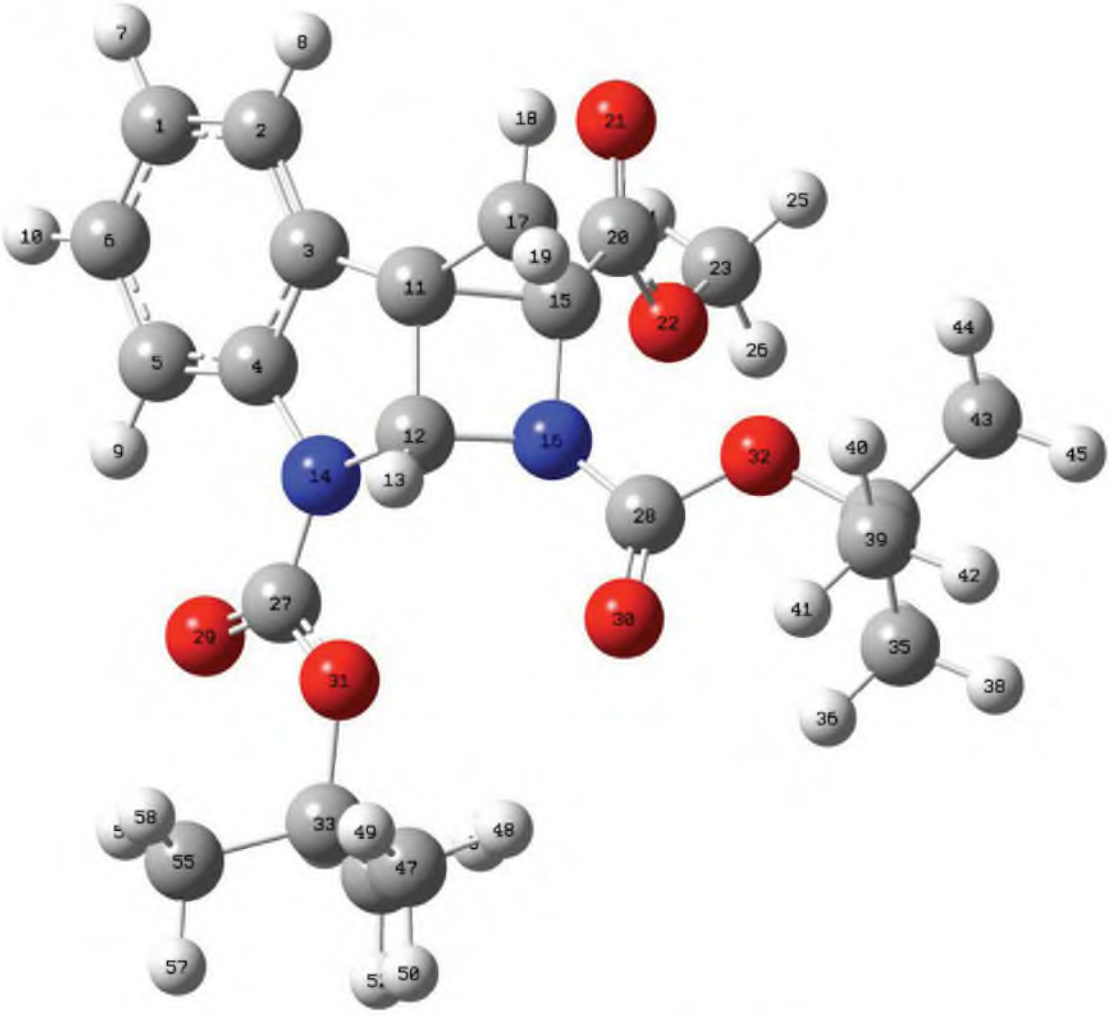


Figure 1.4. Lowest Energy Structure of Cyclopropylazetoindoline **1.170**

nucleophiles to form quaternary substituted carbon centers is not a well known process due to the significant amount of steric crowding around the carbon nucleus. However, there are some unique examples of S_N2 reactions occurring at tertiary carbon centers.[18]

The structural assignment of compound **1.170** was determined by spectroscopic analysis due to the inability to obtain a crystal suitable for X-ray crystallographic analysis. The ^1H NMR displayed nonconventional chemical shifts for the methylene protons in the cyclopropane ring. Typically, the chemical shifts of methylene protons directly attached to a cyclopropane ring fall between the range of 0-1 ppm, whereas the typical chemical shifts for methylene protons in an alkyl chain containing electronegative substituents (e.g. the methylene protons in **1.177**) fall between the range of 2-3 ppm (Figure 1.5). The chemical shifts of H(18) and H(19) for compound **1.170** (numbering given in Figure 1.4) are 2.80 and 2.22 ppm, respectively.

This unusually large chemical shift can be explained by examining the amount of carbocation character on C(11) of compound **1.170** (numbering given in Figure 1.4). Given the push-pull nature of this cyclopropane (refer to **1.182**) combined with a calculated C(11)-C(15) bond length of 1.57 Å (numbering given in Figure 1.4), it is predicted that C(11) should exhibit a high degree of carbocationic character. This property is significant because it would explain the large chemical shift of the methylene protons in **1.170**; the strong carbocationic character of C(11) would serve to deshield the methylene protons on C(17) (Figure 1.5).[19]

We also examined the one bond proton-carbon coupling constants ($^1J_{CH}$) of the methylene protons on **1.170** and found that they were 170.9 Hz and 168.7 Hz. This is significant because the $^1J_{CH}$ can be highly diagnostic for assigning protons attached to a

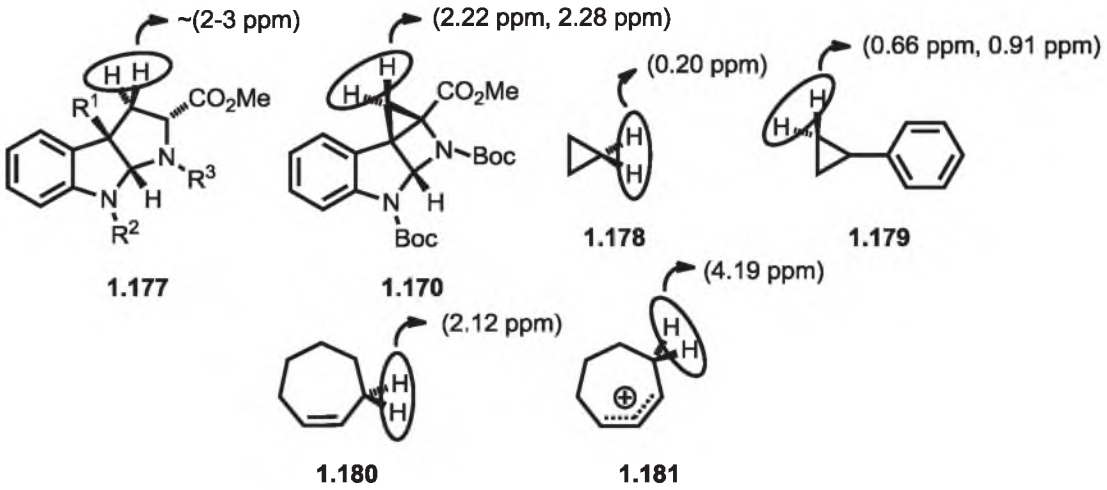
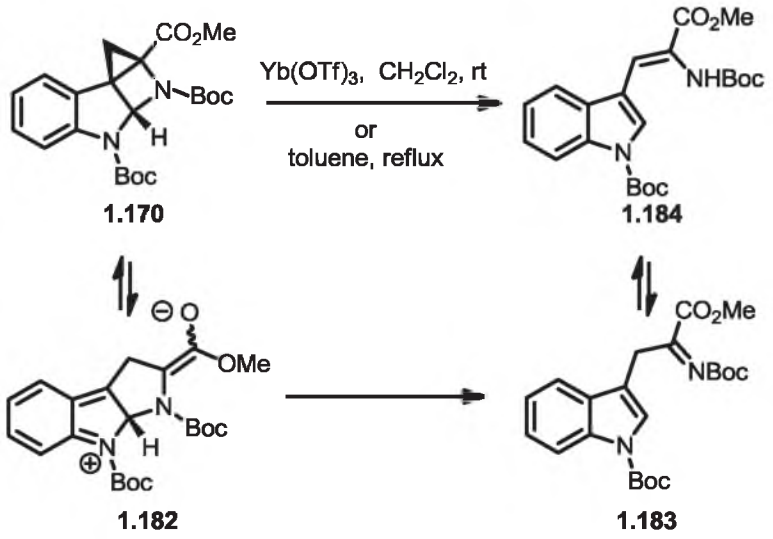


Figure 1.5. Chemical Shifts of Selected Methylene Protons

cyclopropyl ring; typical $^{1}J_{CH}$ values for cyclopropyl protons are about 170 Hz whereas typical $^{1}J_{CH}$ values for alkyl protons are about 125 Hz. These data, combined with the products arising from the addition of nucleophiles to the isolated compound, support the cyclopropane structure given in **1.170**.

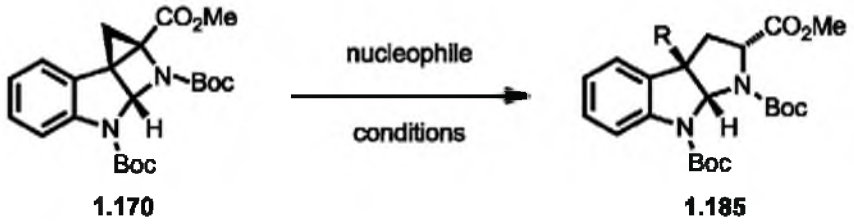
Reactivity of the Cyclopropylazetoindoline

With ready access to gram quantities of cyclopropylazetoindoline **1.170** we next surveyed its reactivity with nucleophiles and its decomposition pathway. We found that **1.170** could be converted to **1.184** through a proposed pathway that reflects the donor-acceptor nature of the cyclopropane (Scheme 1.29). Next, we attempted the direct introduction of a nucleophile to **1.170** and were pleased to find that **1.170** could be made to react quite readily with a variety of nucleophiles under very mild conditions and all products were obtained as the *endo* isomer (Table 1.3).

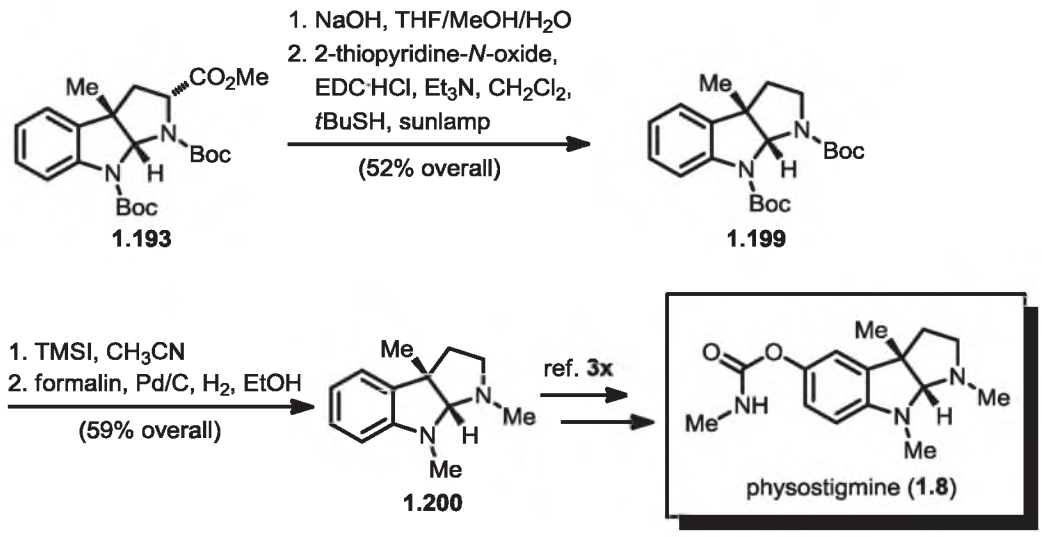


Scheme 1.29. Proposed Decomposition Pathway of **1.170** to **1.184**

Table 1.3. Reaction of Cyclopropylazetoindoline **1.170** with Nucleophiles



entry	nucleophile (eq)	conditions	R (product)	yield (%)
1	indole (1.5)	THF:DMF (2:1)	*N*-indolyl (**1.149**)	70
2	**$NaBH_4$ (10)**	**THF, rt, 2 h**	**H (1.186)**	**75**
3	NaN_3 (10)	PPTS, DMF, rt, 2 h	N_3 (**1.187**)	72
4	**C_6H_5OH (5)**	**DBU, THF, rt, 6 h**	**C_6H_5O (1.188)**	**70**
5	*p*-$MeOC_6H_4OH$ (5)	DBU, THF, rt, 6 h	*p*-$MeOC_6H_4O$ (**1.189**)	76
6	***p*-$NO_2C_6H_4OH$ (5)**	**DBU, THF, rt, 6 h**	***p*-$NO_2C_6H_4O$ (1.190)**	**70**
7	C_6H_5SH (5)	DBU, THF, rt, 6 h	C_6H_5S (**1.191**)	84
8	***p*-$NO_2C_6H_4SH$ (5)**	**DBU, THF, rt, 6 h**	***p*-$NO_2C_6H_4S$ (1.192)**	**80**
9	$AlMe_3$ (2)	CH_2Cl_2, -40 to 0°C, 0.5 h	Me (**1.193**)	76
10	**KCN (10)**	**PPTS, 18-crown-6, THF, rt, 4 h**	**CN (1.194)**	**70**
11	CH_3NO_2	DBU, THF:CH_3NO_2 (4:1), rt, 2 h	CH_2NO_2 (**1.195**)	50
12	**$NCCH_2CN$ (10)**	**DBU, THF, rt, 6 h**	**NCCHCN (1.196)**	**60**
13	methyl acetoacetate (5)	DBU, THF, rt, 6 h	$CH_3C(O)CHCO_2Me$ (**1.197**)	75
14	***p*-MeC_6H_4MgBr, CuCN (5)**	**THF, -78°C, 15 min**	***p*-MeC_6H_4 (1.198)**	**70**



Scheme 1.30. Enantioselective Formal Synthesis of (–)-Physostigmine

Gratifyingly, we were able to obtain a wide range of C(3)-carbon substituted products (entries 9-14, Table 1.3). The importance of the ability to obtain C(3)-carbon substituted pyrroloindolines was discussed above (Figure 1.1).

Enantioselective Formal Synthesis of (–)-Physostigmine

In order to show the utility of the cyclopropylazetoindoline methodology, we completed a formal total synthesis of reversible cholinesterase inhibitor (–)-physostigmine (Scheme 1.30).[3x] To this end, methyl adduct **1.193** underwent a Barton decarboxylation to afford **1.199**, and *N*,*N*′-dimethyl-pyrrolodindoline **1.200** was obtained after protecting group removal and reductive amination of the bis-amine. Synthesis of **1.200** intercepts Kulkarni and coworkers' intermediate.

Conclusions

We have demonstrated a new synthesis of C(3)-quaternary substituted indolines that employs a novel reaction of bromopyrroloindolines. This unique reaction is very useful in terms of the substrates generated and the types of nucleophiles that may be added to the generated cyclopropylazetoindoline. Additionally, we have shown the utility of this technology in performing an enantioselective formal synthesis of (–)-physostigmine. Further work will be done in the pursuit of establishing the exact reaction mechanism that the cyclopropylazetoindoline undergoes upon addition of nucleophiles.

Experimental Section

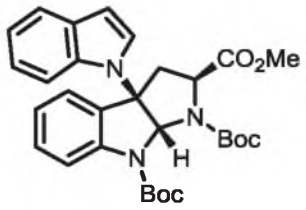
Chemicals were either used as received or purified according to *Purification of Common Laboratory Chemicals*.[20] Glassware was dried in an oven at 130 °C or flame dried and cooled under a dry atmosphere prior to use. All reactions were performed using common dry, inert atmosphere techniques. Reactions were monitored by TLC and visualized by a dual short wave/long wave UV lamp and stained with an ethanolic solution of potassium permanganate or p-anisaldehyde. Column flash chromatography was performed using 230-400 mesh silica gel. NMR spectra were recorded on Varian Unity-300, Varian VXR-500, or Varian Inova-500 spectrometers. Chemical shifts for ^{1}H NMR were reported as δ, parts per million, relative to the signal of tetramethylsilane at 0 ppm. Chemical shifts for ^{13}C NMR were reported as δ, parts per million, relative to the center line signal of the $CDCl_3$ triplet at 77 ppm. Proton and carbon assignments were established using spectral data of similar compounds, ^{1}H nOe analysis, and ^{13}C DEPT NMR. The abbreviations s, bs, d, dd, bd, ddd, t, q, bq, and m stand for the resonance

multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, and multiplet, respectively. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Optical rotations were obtained on a Perkin Elmer Model 343 polarimeter (Na D line) using a microcell with a 1 decimeter path length. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 double focusing high resolution mass spectrometer. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg).

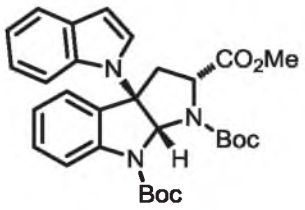
1.201 **1.148**

Preparation of (2*S*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-bromo-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.148). To a solution of bis-Boc protected tryptophan **1.201** (0.169 g, 0.40 mmol) in methylene chloride (4 mL) at rt was added PPTS (0.102 g, 0.40 mmol) and NBS (0.073 g, 0.40 mmol). After stirring for 8 h the solution was diluted with CH_2Cl_2 (20 mL) and washed with brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography (5-10% EtOAc:hexanes) afforded 0.186 g (92%) of **1.148** as a white foam. **1.148**: R_f 0.30 (20% EtOAc:hexanes); $[\alpha]^{25}_D = -157.3$ (c = 0.635, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (broad s, 1H), 7.37-7.30 (m, 2H), 7.13 (dd, J = 7.5 Hz, 7.5 Hz, 1H), 6.40 (s, 1H), 3.89 (dd, J = 10.2 Hz, 6.0 Hz, 1H), 3.75 (s, 3H), 3.21 (dd, J = 12.6, 6.3 Hz, 1H), 2.82 (dd, J =

12.6 Hz, 10.2 Hz, 1H), 1.60 (s, 9H), 1.40 (bs, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (broad), 152.2, 152.2, 141.5, 132.9 (broad), 130.6, 124.4 (broad), 123.2, 118.5 (broad), 83.8, 82.2, 81.5 (broad), 59.7 (broad), 59.4, 52.3, 41.9 (broad), 28.2, 28.2; IR (neat) 2980, 1754, 1720, 1604, 1478, 1396, 1367, 1335, 1258, 1204, 1163 cm^{-1}; LRMS (ESI) calcd for $C_{22}H_{30}N_2O_6Br$ *m/z* ($M+H^+$) 497.1, found 496.9.



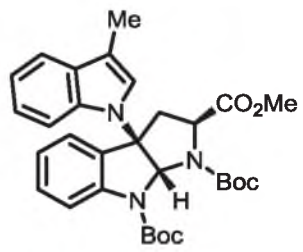
1.149-*exo*



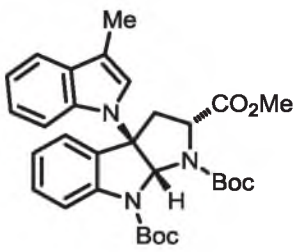
1.149-*endo*

Preparation of (2*S*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.149-*exo*) and (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.149-*endo*). To a solution of **1.148** (0.196 g, 0.39 mmol) and **1.151** (0.031 g, 0.26 mmol) in CH_3CN (8 mL) at 0 °C was added KOtBu (0.52 mL, 1M in THF) dropwise and the mixture stirred for 20 min. The mixture was quenched with sat. $NaHCO_3$ (1 mL) and diluted with CH_2Cl_2 (60 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (10% EtOAc:hexanes) afforded 0.019 g (14%) of **1.149**-*exo* and 0.091 g (65%) of **1.149**-*endo*. **1.149**-*exo*: white foam; R_f 0.28 (10% EtOAc:hexanes); $[\alpha]_D$ = +60.4 (*c* = 0.605); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.58 (partially obscured m, 1 H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.50-7.42 (m, 2H), 7.31-7.12 (m, 3H), 6.81 (s, 1H), 6.70 (broad d, *J* = 3.3 Hz, 1H), 6.35 (d, *J* = 3.6 Hz, 1H), 4.12 (dd, *J* = 9.9, 7.2 Hz, 1H), 3.80 (s,

3H), 3.34 (dd, J = 12.9, 10.5 Hz, 1H), 2.94 (dd, J = 12.9, 7.2 Hz, 1H), 1.44 (s, 9H), 1.40 (broad s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 152.1, 152.1, 142.8, 134.4, 131.0, 130.5, 130.2 (broad), 126.5, 125.1, 124.1, 122.2, 121.5, 120.2, 119.2 (broad), 111.7, 101.8, 82.2, 81.4 (broad), 78.9, 71.4 (broad), 59.2, 52.4, 36.3 (broad), 28.2, 28.0; IR (neat) 2978, 1604, 1481, 1396, 1336, 1160, 1018 cm^{-1}; LRMS (ESI) calcd for $C_{30}H_{36}N_3O_6$ *m/z* ($M+H^+$) 534.3, found 534.1. **1.149**-*endo*: R_f 0.20 (10% EtOAc:hexanes); white foam; $[\alpha]_D$ = +82.8 (*c* = 0.115); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (broad s, 1H), 7.63-7.60 (m, 1H), 7.40-7.28 (m, 3H), 7.22-7.06 (m, 3H), 6.96 (broad d, J = 3.3 Hz, 1H), 6.81 (s, 1H), 6.41 (dd, J = 3.3, 0.6 Hz, 1H), 4.91 (broad d, J = 8.1 Hz, 1H), 3.55 (dd, J = 12.9, 9.3 Hz, 1H), 3.23 (s, 3H), 3.04 (d, J = 13.2 Hz, 1H), 1.52 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 153.3 (broad), 152.0, 143.6, 134.5, 130.9, 130.5, 129.2 (broad), 126.2, 125.4 (broad), 123.3 (broad), 122.0, 121.5, 120.1, 117.8 (broad), 111.1, 102.0, 82.0, 81.4 (broad), 79.9, 72.6 (broad), 59.4 (broad), 52.1, 38.6 (broad), 28.3, 28.1; IR (neat) 2979, 1716, 1604, 1481, 1393, 1160, 1018 cm^{-1}; LRMS (ESI) calcd for $C_{30}H_{36}N_3O_6$ *m/z* ($M+H^+$) 534.3, found 534.2.



1.157-*exo*

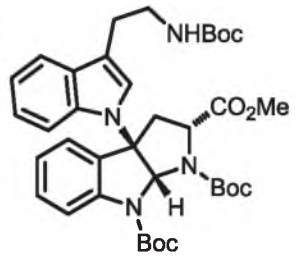


1.157-*endo*

Preparation of (2*S*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(3-methyl-1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.157-*exo*) and (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(3-methyl-1*H*-indol-1-yl)-3,3a-

dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.157-*endo*). To a solution of **1.148** (0.082 g, 0.17 mmol) and **1.152** (0.015 g, 0.11 mmol) in CH_3CN (3 mL) at 0 °C was added KOtBu (0.22 mL, 1M in THF) dropwise and stirred for 20 min. The mixture was quenched with sat. $NaHCO_3$ (1 mL) and diluted with CH_2Cl_2 (60 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (10% EtOAc:hexanes) afforded 0.012 g (20%) of **1.157**-*exo* and 0.037 g (61%) of **1.157**-*endo*. **1.157**-*exo*: white foam; R_f 0.26 (10% EtOAc:hexanes); $[\alpha]_D$ = +44.1 (*c* = 0.303); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (bs, 1H), 7.58-7.42 (m, 4H), 7.29-7.12 (m, 3H), 6.77 (s, 1H), 6.48 (s, 1H), 4.10 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.80 (s, 3H), 3.30 (dd, *J* = 12.6, 10.2 Hz, 1H), 2.94 (dd, *J* = 12.6, 7.2 Hz, 1H), 2.16 (s, 3H), 1.44 (bs, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 152.2, 152.2, 142.8, 134.8, 130.9, 130.9, 130.4 (broad), 125.0, 124.0, 124.0 (broad), 122.2, 119.5, 119.5, 119.2 (broad), 111.6, 110.8 (broad), 82.1, 81.5 (broad), 79.1, 71.3 (broad), 59.2, 52.4, 36.3 (broad), 28.2, 28.0, 9.4; IR (neat) 2980, 1720, 1606, 1481, 1456, 1397, 1344, 1264, 1161, 1019, 907, 857 cm^{-1}; LRMS (ESI) calcd for $C_{31}H_{38}N_3O_6$ *m/z* ($M+H^+$) 548.3, found 548.1. **1.157**-*endo*: white foam; R_f 0.19 (10% EtOAc:Hexanes); $[\alpha]_D$ = +41.6 (*c* = 0.202); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (bs, 1H), 7.54 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.39-7.05 (m, 6H), 6.77 (s, 1H), 6.73 (s, 1H), 4.89 (broad d, *J* = 8.4 Hz, 1H), 3.51 (dd, *J* = 12.6, 9.3 Hz, 1H), 3.22 (s, 3H), 3.04 (d, *J* = 12.9, 1H), 2.21 (s, 3H), 1.52 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 153.2 (broad), 152.0, 143.5, 134.9, 130.8, 130.7, 129.6 (broad), 125.4 (broad), 123.7, 123.3 (broad), 122.0, 119.5, 119.4, 117.9 (broad), 111.3, 111.0, 82.0, 81.4 (broad), 80.0, 72.5 (broad), 59.5 (broad), 52.1, 38.7 (broad), 28.3, 28.2, 9.4; IR (neat) 2978, 1717, 1652, 1606, 1559, 1541, 1481, 1394, 1258, 1159, 1019 cm^{-1}; LRMS (ESI)

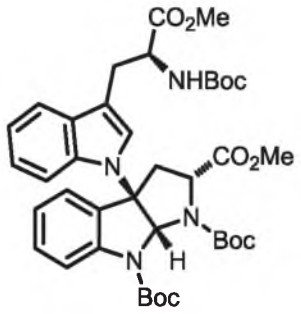
calcd for $C_{31}H_{38}N_3O_6$ *m/z* ($M+H^+$) 548.3, found 548.1.



1.158

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.158). To a solution of **1.148** (0.308 g, 0.62 mmol) and **1.153** (0.108 g, 0.41 mmol) in CH_3CN (12 mL) at 0 °C was added KOtBu (0.82 mL, 1M in THF) dropwise and stirred for 30 min. The mixture was quenched with sat. $NaHCO_3$ (1 mL) and diluted with CH_2Cl_2 (100 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (20% EtOAc:hexanes) afforded 0.135 g (48%) of **1.158**. **1.158**: white foam; R_f 0.18 (20% EtOAc:hexanes); $[\alpha]_D$ = +33.0 (*c* = 0.283); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (bs, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.40-7.06 (m, 6H), 6.78 (s, 1H), 6.77 (s, 1H), 4.90 (bd, *J* = 8.7 Hz, 1H), 4.58 (bs, 1H), 3.52 (dd, *J* = 12.9, 9.3 Hz, 1H), 3.34 (broad dt, *J* = 6.3, 6.0 Hz, 2H), 3.23 (s, 3H), 3.02 (d, *J* = 13.2 Hz, 1H) 2.83 (t, *J* = 6.9 Hz, 2H), 1.52 (s, 9H), 1.50 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 155.9, 152.0, 152.0, 143.5, 135.0, 130.9, 130.0, 129.2 (broad), 125.4 (broad), 124.0, 123.4 (broad), 122.2, 119.8, 119.6, 117.9 (broad), 112.5, 111.5, 82.1, 81.5 (broad), 79.8, 79.1 (broad), 72.5 (broad), 59.4 (broad), 52.1, 40.9 (broad) 38.6 (broad), 28.4, 28.3, 28.2, 25.7 (broad); IR (neat) 3397, 2979, 2930, 1755,

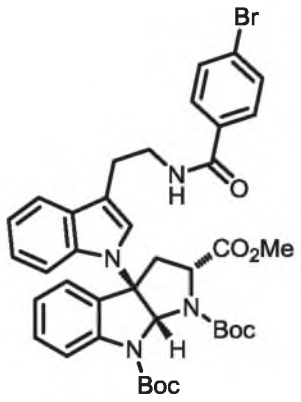
1711, 1605, 1507, 1482, 1457, 1394, 1265, 1164 cm^{-1}; LRMS (ESI) calcd for $C_{37}H_{49}N_4O_8$ *m/z* ($M+H^+$) 677.3, found 677.2.



1.159

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.159). To a solution of **1.148** (0.111 g, 0.22 mmol) and **1.154** (0.047 g, 0.15 mmol) in CH_3CN (4 mL) at 0 °C was added KOtBu (0.30 mL, 1M in THF) dropwise and stirred for 30 min. The mixture was quenched with sat. $NaHCO_3$ (1 mL) and diluted with CH_2Cl_2 (100 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (20-25% EtOAc:hexanes) afforded 0.043 g (39%) of **1.159**. **1.159**: white foam; R_f 0.28 (33% EtOAc:hexanes); $[\alpha]_D$ = +50.7 (*c* = 1.389); ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (broad s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.39-7.06 (m, 6H), 6.77 (s, 1H), 6.71 (bs, 1H), 5.05 (broad d, *J* = 7.2 Hz, 1H), 4.91 (broad d, *J* = 8.7 Hz, 1H), 4.60-4.50 (m, 1H), 3.59-3.50 (m, 4H), 3.22 (s, 3H), 3.22-2.97 (partially obscured m, 3H), 1.53 (s, 9H), 1.51 (s, 9H), 1.42/1.40 (Boc rotamers, two singlets, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (Note: Boc-rotamers give duplicities on some carbons) 172.3, 172.2, 170.8, 154.8, 152.9 (broad), 151.8, 143.5, 143.4, 134.6, 130.8, 130.8, 130.3, 130.2, 129.2. 128.9

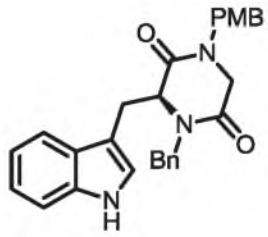
(broad), 125.2 (broad), 124.7, 123.2, 123.2 (broad), 122.2, 119.8, 119.4, 118.0 (broad), 111.3, 109.6, 109.5, 81.9, 81.9, 81.2 (broad), 79.7, 79.7, 79.5 (broad), 72.5 (broad), 59.3 (broad), 55.1, 54.1, 52.0, 51.9, 51.8, 38.5 (broad), 28.2, 28.0, 27.7 (broad); IR (neat) 3438, 2979, 1715, 1605, 1483, 1393, 1164, 1062, 1019, 916, 856 cm^{-1}; LRMS (ESI) calcd for $C_{39}H_{51}N_4O_{10}$ *m/z* ($M+H^+$) 735.4, found 735.0.



1.160

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(3-(2-(4-bromobenzamido)ethyl)-1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.160). To a solution of **1.148** (0.586 g, 1.18 mmol) and **1.155** (0.270 g, 0.79 mmol) in CH_3CN (23 mL) at 0 °C was added KOtBu (1.51 mL, 1M in THF) dropwise and stirred for 30 min. The mixture was quenched with sat. $NaHCO_3$ (1 mL) and diluted with CH_2Cl_2 (120 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (30% EtOAc:hexanes) afforded 0.462 g (78%) of **1.160**. **1.160**: white foam; R_f 0.17 (33% EtOAc:hexanes); $[\alpha]_D$ = +24.8 (*c* = 0.582); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (broad s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.49 (s, 4H), 7.37 (dd, *J* = 7.8, 7.8 Hz, 1 H), 7.30-7.18 (m, 3 H), 7.12 (dd, *J* =

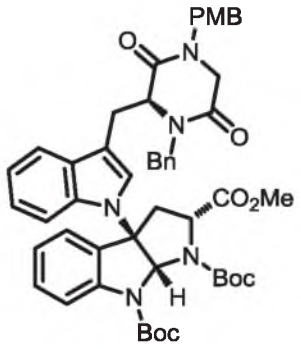
7.2, 7.2 Hz, 1 H), 7.04 (dd, J = 7.5, 7.5 Hz, 1 H), 6.81 (s, 1H), 6.79 (s, 1H), 6.32-6.24 (m, 1H), 4.90 (broad d, J = 8.4 Hz, 1H), 3.65 (dt, J = 6.3, 6.3 Hz, 2H) 3.50 (dd, J = 13.2, 9.6 Hz, 1H), 3.22 (s, 3H), 3.03 (d, J = 13.2 Hz, 1H), 2.95 (t, J = 6.3 Hz, 2H), 1.51 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 166.3, 153.2 (broad), 152.0, 143.4, 135.0, 133.4, 131.7, 130.9, 129.9, 129.2 (broad), 128.4, 125.9, 125.3 (broad), 124.0, 123.4 (broad), 122.4, 119.9, 119.5, 117.8 (broad), 112.4, 111.6, 82.2, 81.4 (broad), 79.9, 72.6 (broad), 59.4 (broad), 52.1, 40.4, 38.6 (broad), 28.3, 28.2, 25.0; IR (neat) 3357, 2978, 1718, 1648, 1593, 1538, 1481, 1394, 1260, 1158, 1069, 1015, 912, 853 cm^{-1}; LRMS (ESI) calcd for $C_{39}H_{44}BrN_4O_7$ *m/z* ($M+H^+$): 781.2, found 780.9.



1.156

Preparation of (*S*)-3-((1*H*-indol-3-yl)methyl)-4-benzyl-1-(4-methoxybenzyl)piperazine-2,5-dione (1.156). To a solution of *N*-benzyl protected L-tryptophan methyl ester (0.306 g, 0.99 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.28 mL, 1.98 mmol) followed by a solution of chloroacetyl chloride (0.134 g, 1.19 mmol) in CH_2Cl_2 (2 mL) dropwise. The resulting mixture was stirred at 0 °C for 6 h and then the reaction was quenched with 10% aq. $NaHCO_3$ (20 mL). The organic phase was washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated. The resulting residue was taken up in CH_3CN (9 mL) and to this was added 4-methoxy-benzylamine (0.379 g, 2.76 mmol). The reaction mixture was heated to reflux for 6 h.

After cooling, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed sequentially with 10% $KHSO_4$ (20 mL), H_2O (20 mL), brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography (50% EtOAc:hexanes) afforded 0.337 g (75% overall) of **1.156** as an oil. **1.156**: clear oil; R_f 0.25 (33% EtOAc:hexanes); $[\alpha]_D = -42.1$ (*c* = 0.580); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (bs, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.38-7.11 (m, 8H), 6.77-6.67 (m, 5H), 5.44 (d, *J* = 14.7 Hz, 1 H), 4.52 (d, *J* = 14.4 Hz, 1H), 4.26 (t, *J* = 3.6 Hz, 1H), 4.01 (d, *J* = 14.7 Hz, 1H), 3.73 (s, 3H), 3.56-3.50 (m, 2 H), 3.26 (partially obscured dd, *J* = 15.0, 4.5 Hz, 1H), 3.25 (d, *J* = 17.4 Hz, 1H), 2.24 (t, *J* = 17.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 165.0, 159.1, 136.0, 135.3, 129.6, 128.9, 128.4, 128.1, 127.1, 126.6, 124.1, 122.4, 119.9, 118.9, 114.0, 111.2, 108.3, 59.9, 55.2, 48.4, 48.0, 46.8, 26.8; IR (neat) 3299, 2930, 1658, 1513, 1468, 1325, 1248, 1176, 1101, 1032, 974, 817 cm^{-1}; LRMS (ESI) calcd for $C_{28}H_{28}N_3O_3$ *m/z* ($M+H^+$) 454.2, found 454.2.

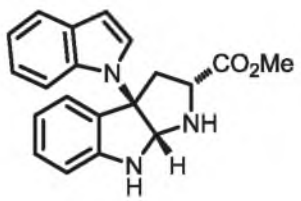


1.161

Preparation of (2*S*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(3-(((*S*)-1-benzyl-4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.161). To a solution of

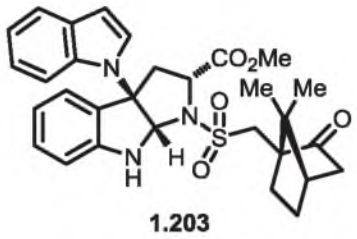
1.148 (0.199 g, 0.40 mmol) and **1.156** (0.121 g, 0.267 mmol) in CH_3CN (8 mL) at 0 °C was added KOtBu (0.53 mL, 1M in THF) dropwise and stirred for 20 min. The mixture was quenched with sat. $NaHCO_3$ (1 mL) and diluted with CH_2Cl_2 (120 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (33% EtOAc:hexanes) afforded 0.177 g (76%) of **1.161** as 4.8:1 mixture of *endo*:*exo* isomers. The endo isomer of **1.161** was characterized from a 14:1 mixture of endo:exo diastereomers (from the reaction of **1.156** (1.2 eq) with **1.148** (1.0 eq) and KO*t*Bu (1.2 eq.) at 0 °C for 30 s, 17% yield); white foam; R_f 0.25 (33% EtOAc:hexanes); $[\alpha]_D = -14.7$ (*c* = 0.218); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.60 (partially obscured m, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.45-7.39 (m, 2H), 7.33-7.14 (m, 9H), 6.83 (s, 1H), 6.74-6.66 (m, 4H), 6.62 (s, 1H), 5.26 (d, *J* = 14.7 Hz, 1H), 4.90-4.84 (partially obscured m, 1H), 4.55 (d, *J* = 14.4 Hz, 1H), 4.18 (broad dd, *J* = 3.9 Hz, 3.0 Hz, 1H), 3.96 (d, *J* = 15.0 Hz, 1H), 3.76 (s, 3H), 3.46-3.39 (m, 2H), 3.29-3.21 (partially obscured m, 2H), 3.21 (s, 3H), 3.00 (dd, *J* = 15.0 Hz, 4.5 Hz, 1H), 2.85 (d, *J* = 13.2 Hz, 1H), 2.05 (d, *J* = 17.4 Hz, 1H), 1.51 (bs, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (broad), 166.1, 164.9, 159.2, 159.2, 151.9 (broad), 143.8, 135.4, 134.3, 131.2, 129.9, 129.7, 129.7, 128.9, 128.9, 128.5, 128.5, 128.1, 126.5, 126.5, 123.5 (broad), 122.8, 120.5, 120.0, 114.0, 111.5, 107.7, 82.1, 82.1, 79.2, 72.4 (broad), 59.8, 59.4 (broad), 55.2, 52.1, 48.3, 48.0, 46.8, 38.4 (broad), 28.3, 28.2, 26.4; IR (neat) 2977, 1755, 1717, 1663, 1610, 1553, 1513, 1458, 1393, 1368, 1330, 1250, 1209, 1160, 1062, 854 cm^{-1}; LRMS (ESI) calcd for $C_{50}H_{55}N_5O_9Na$ *m/z* ($M+Na^+$): 892.4, found 892.1.

Enantiopurity of **1.149**-*endo* was established through derivatization with (1*S*)-(+)-camphorsulphonyl chloride as a chiral resolving agent:



1.202

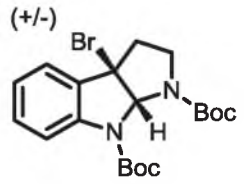
Preparation of (2*R*,3a*R*,8a*R*)-methyl 3a-(1*H*-indol-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (1.202). To a solution of heterodimer **1.149**-*endo* (0.125 g, 0.230 mmol) in CH_3CN (5 mL) at 0 °C was added dropwise TMSI (0.08 mL, 0.58 mmol). The reaction mixture turned a dark yellow color and was quenched after 30 min with sat. $NaHCO_3$ (2 mL). The organic phase was washed with H_2O (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (75% EtOAc:hexanes) afforded 0.049 g (63%) of **1.202** as a colorless oil. **1.202**: oil; R_f 0.07 (50% EtOAc:hexanes); $[\alpha]_D$ = +13.4 (*c* = 0.294); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7 7.62-7.59 (m, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1 H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1 H), 7.18-7.06 (m, 3H), 6.76 (t, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1 H), 6.45 (d, *J* = 3.3 Hz, 1H), 5.52 (s, 1H), 4.50 (bs, 1H), 4.21 (dd, *J* = 7.8, 2.4 Hz, 1H), 3.48 (dd, *J* = 13.2, 7.8 Hz, 1 H), 3.36 (s, 3 H), 2.95 (dd, *J* = 13.2, 2.7 Hz, 1H), 2.62 (broad s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 149.7, 134.9, 130.4, 130.3, 127.7, 126.1, 125.5, 121.6, 121.2, 119.7, 119.4, 112.0, 110.8, 101.2, 81.9, 75.8, 60.3, 52.0, 40.6; IR (neat) 3363, 2950, 1736, 1609, 1459, 1321, 1225, 1121, 1018, 960, 891 cm^{-1}; LRMS (ESI) calcd for $C_{20}H_{20}N_3O_2$ *m/z* ($M+H^+$) 334.1, found 334.0.



1.203

Preparation of (2*R*,3a*R*,8a*S*)-methyl 1-((((1*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methyl)sulfonyl)-3a-(1*H*-indol-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (1.203). To a solution of bis-amine **1.203** (0.024 g, 0.070 mmol), Et_3N (0.015 mL, 0.11 mmol), and DMAP (0.001 g, 0.01 mmol) in THF (3.6 mL) at 0 °C was added (1*S*)-(+)-camphorsulfonyl chloride (0.020 g, 0.080 mmol). The reaction mixture was stirred for 1 h at 0 °C, diluted with CH_2Cl_2 (60 mL), and washed sequentially with 10% $KHSO_4$ (20 mL), 10% $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated. In addition to unreacted starting material, only a single diastereomer of the product could be detected from the crude ^1H NMR. Flash chromatography (15-20% EtOAc:hexanes) afforded 0.027 g (68%) of **1.203** as a white foam. **1.203**: white foam; R_f 0.74 (50% EtOAc:hexanes); $[\alpha]_D$ = +8.1 (*c* = 0.248); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.29-7.19 (m, 3H), 7.12 (dd, *J* = 7.2, 7.2 Hz, 1 H), 6.98 (d, *J* = 3.3 Hz, 1H), 6.89 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.41 (d, *J* = 3.6 Hz, 1H), 6.19 (d, *J* = 1.2 Hz, 1H), 5.21 (broad s, 1H), 4.97 (dd, *J* = 7.8, 1.2 Hz, 1H), 3.75 (d, *J* = 15.0 Hz, 1H), 3.72 (dd, *J* = 13.8, 9.3 Hz, 1H), 3.33 (s, 3H), 3.32 (partially obscured d, *J* = 14.7 Hz, 1H), 3.11 (d, *J* = 13.8 Hz, 1H), 2.47-2.34 (m, 2H), 2.11 (dd, *J* = 4.2, 4.2 Hz, 1H), 2.12-1.98 (partially obscured m, 1H), 1.93 (d, *J* = 18.3 Hz, 1H), 1.65 (ddd, *J* = 13.8, 9.3, 4.5 Hz, 1H), 1.40 (ddd, *J* = 12.6, 9.6, 3.9 Hz, 1H), 1.14 (s, 3H), 0.97

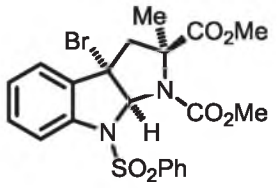
(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2, 171.3, 150.0, 134.7, 131.7, 130.7, 126.5, 126.2, 125.9, 122.4, 121.8, 120.4, 120.1, 111.9, 111.9, 102.1, 81.2, 75.8, 61.1, 59.2, 52.7, 52.3, 47.9, 43.6, 43.0, 39.8, 27.0, 27.0, 20.5, 20.2; IR (neat) 3380, 2957, 1744, 1611, 1456, 1338, 1223, 1156, 1039, 859, 740 cm^{-1}; LRMS (ESI) calcd for $C_{30}H_{34}N_3O_5S$ *m/z* ($M+H^+$) 548.2, found 548.0.



1.163

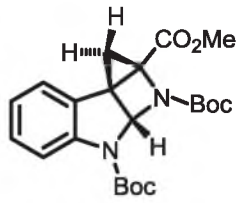
Preparation of di-*tert*-butyl 3a-bromo-3,3a-dihydropyrrolo[2,3-*b*]indole-1,8(2*H*,8a*H*)-dicarboxylate (1.163). To a solution of bis-Boc protected tryptamine **1.162** (0.999 g, 2.77 mmol) in CH_2Cl_2 (28 mL) at rt was added PPTS (0.697 g, 2.77 mmol) and NBS (0.498 g, 2.77 mmol). After stirring for 4 h the solution was diluted with CH_2Cl_2 (25 mL) and washed with brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography (5-10% EtOAc:hexanes) afforded 0.811 g (67%) of **1.163**. **1.163**: white foam; R_f 0.50 (10% EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (broad d, J = 5.7 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.31-7.25 (m, 1H), 7.08 (dt, J = 7.8, 1.2 Hz, 1H), 6.44 (s, 1H), 3.73 (dd, J = 9.6, 6.9 Hz, 1H), 2.85-2.69 (m, 3H), 1.59/1.58 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 151.9, 141.9, 132.5 (broad), 130.1, 123.9, 123.6, 117.2 (broad), 83.7, 81.9, 80.5 (broad), 62.0, 46.0, 41.3 (broad), 28.2, 28.1; IR (neat) 2977, 1715, 1652, 1605, 1558, 1541, 1478, 1394, 1256, 1155, 1018, 850 cm^{-1}; LRMS (ESI) calcd for $C_{20}H_{28}BrN_2O_4$ *m/z* ($M+H^+$) 438.1, found

438.9.



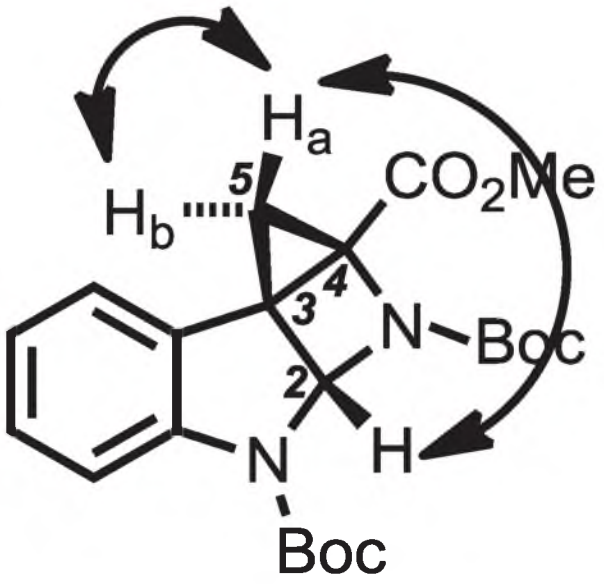
1.174

Preparation of (2*S*,3a*S*,8a*S*)-dimethyl 3a-bromo-2-methyl-8-(phenylsulfonyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylate (1.174). A solution of pyrroloindoline **1.173** (0.169 g, 0.39 mmol), NBS (0.071 g, 0.39 mmol), and AIBN (0.006 g, 0.04 mmol) in CCl_4 (8 mL) were heated at reflux for 2.5 h. The resulting heterogeneous mixture was cooled to room temperature and concentrated. Flash chromatography (33% EtOAc:hexanes) afforded 0.156 g (78%) of **1.174**. **1.174**: white foam; R_f 0.37 (33% EtOAc:hexanes); $[\alpha]^{25}_D$ = +96.0 (*c* = 0.316, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.80 (m, 2H), 7.53-7.47 (m, 2H), 7.42-7.29 (m, 3H), 7.22-7.19 (m, 1H), 7.15-7.10 (m, 1H), 6.39 (s, 1H), 3.64 (s, 3H), 3.40 (d, *J* = 13.2 Hz, 1H), 3.05 (s, 3H), 2.80 (d, *J* = 13.5 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 153.3, 153.3, 141.8, 139.3, 133.8, 133.2, 130.8, 128.8, 127.5, 125.7, 124.3, 118.5, 88.5, 67.1, 57.7, 53.0, 52.3, 52.2, 25.1; IR (neat) 3065, 2953, 1751, 1724, 1601, 1444, 1367, 1291, 1222, 1169 cm^{-1}; LRMS (ESI) calcd for $C_{21}H_{22}N_2O_6SBr$ *m/z* ($M+H^+$) 509.0, found 508.9.



1.170

Preparation of (1a*R*,2a*S*,7b*R*)-2,3-di-*tert*-butyl 1a-methyl 1*H*-cyclopropa[3,4]azeto[2,3-*b*]indole-1a,2,3(1a*H*,2a*H*)-tricarboxylate (1.170). To a solution of bromide **1.148** (1.00 g, 2.01 mmol) in THF (10 mL) at 0 °C was added KO*t*Bu (2.42 mL of a 1.0 M solution in THF, 2.4 mmol) dropwise over 1 h. The reaction was quenched with sat. aq. NH_4Cl (6 mL) and the resulting mixture was diluted with CH_2Cl_2 (150 mL). After separation, the organic phase was washed with H_2O (25 mL), brine (25 mL), and dried ($MgSO_4$). Concentration afforded 0.799 g (95%) of **1.170** as an amorphous white solid that was used without further purification. **1.170**: R_f 0.33 (20% EtOAc:hexanes); $[\alpha]_D$ = +291.3 (*c* = 0.192, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (bs, 1H), 7.18 (ddd, *J* = 8.2, 7.2, 1.7 Hz, 1H), 6.95 (ddd, *J* = 7.4, 1.7, 0.6 Hz, 1H), 6.92 (ddd, *J* = 7.3, 7.3, 0.9 Hz, 1H), 5.85 (s, 1H), 3.61 (s, 3H), 2.80 (d, *J* = 7.1 Hz, 1H), 2.22 (d, *J* = 7.1 Hz, 1H), 1.58 (s, 9H), 1.48 (s, 9H);^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 156.2, 152.1, 147.7, 128.9, 122.5, 122.3, 121.6, 115.0, 82.5, 81.1, 79.7, 56.3, 52.2, 39.8, 28.4, 28.1, 25.5; IR (neat) 2975, 1711, 1458, 1371, 1317, 1245, 1158, 1101, 1074, 758; HRMS (ESI) calcd for $C_{22}H_{28}N_2O_6Na$ *m/z* ($M+Na^+$) 439.1845, found 439.1857.



1.170

Summary of nOe data for Cyclopropylazetoindoline **1.170** (500 MHz, $CDCl_3$)

1. Irradiation of proton H-2 at 5.85 ppm showed a reciprocal nOe with proton H-5a at 2.22 ppm.

2. Irradiation of proton H-5b at 2.80 ppm showed a reciprocal nOe with proton H-5a at 2.22 ppm.

Lowest Energy Structure Calculations

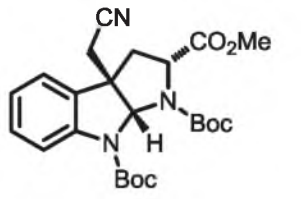
Calculations on **1.170** were completed using the Gaussian09 package[21] using density functional theory (DFT) with the B3LYP exchange and correlation functionals[22] and the 6-311G** basis set.[23] The coordinates of the optimized geometry of this structure are provided below (Table 1.4) (coordinates given in Figure 1.4):

Table 1.4. Coordinates for Energy Minimized Structure of **1.170**

center	atom	X	Y	Z
1	C	-3.937604	-3.325234	-0.430756
2	C	-2.675531	-3.169307	-1.009797
3	C	-2.028922	-1.950357	-0.882879
4	C	-2.624048	-0.883365	-0.180117
5	C	-3.875703	-1.034266	0.405796
6	C	-4.519498	-2.268790	0.265105
7	H	-4.459821	-4.270413	-0.519502
8	H	-2.203260	-3.986253	-1.542124
9	H	-4.326205	-0.220306	0.951680
10	H	-5.497655	-2.398525	0.714608
11	C	-0.705892	-1.494828	-1.316816
12	C	-0.586514	0.013867	-1.025773
13	H	-0.502797	0.732953	-1.840777
14	N	-1.780823	0.263240	-0.207491
15	C	0.641367	-1.665777	-0.528677
16	N	0.686856	-0.223775	-0.321047
17	C	0.491274	-2.062185	-1.981836
18	H	0.484550	-3.135748	-2.126436
19	H	1.013303	-1.487407	-2.741203
20	C	0.860160	-2.684181	0.520767
21	O	0.726600	-3.871197	0.325319
22	O	1.173641	-2.140039	1.705953
23	C	1.344350	-3.075535	2.786977
24	H	0.420036	-3.627564	2.962081
25	H	2.143933	-3.781519	2.557989
26	H	1.600099	-2.470871	3.653863
27	C	-2.157566	1.517747	0.249798
28	C	1.826703	0.556317	-0.430114
29	O	-3.131805	1.717970	0.941983
30	O	1.818486	1.742962	-0.669886
31	O	-1.291614	2.436947	-0.197248
32	O	2.909280	-0.211945	-0.208552
33	C	-1.366487	3.851898	0.239204
34	C	4.266567	0.367775	-0.129393
35	C	4.331323	1.387725	1.009554
36	H	3.718013	2.260736	0.792821
37	H	3.986171	0.934277	1.942009
38	H	5.366140	1.711305	1.149863
39	C	4.652178	0.975415	-1.480183
40	H	4.548090	0.230927	-2.273796
41	H	4.027860	1.835239	-1.717096

Table 1.4. continued

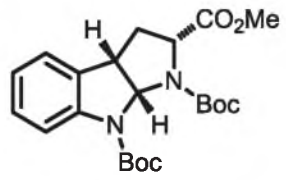
center	atom	X	Y	Z
42	H	5.697149	1.295868	-1.451615
43	C	5.126600	-0.855736	0.185478
44	H	5.035264	-1.602959	-0.605681
45	H	6.176384	-0.565222	0.270234
46	H	4.811995	-1.310119	1.127042
47	C	-0.204411	4.491616	-0.518670
48	H	0.725336	3.965106	-0.304195
49	H	-0.378987	4.444869	-1.596151
50	H	-0.107617	5.541060	-0.229127
51	C	-1.144280	3.923739	1.751108
52	H	-1.102185	4.970543	2.063312
53	H	-1.952086	3.432348	2.292228
54	H	-0.195635	3.450154	2.014553
55	C	-2.702378	4.465481	-0.186986
56	H	-3.536523	4.022805	0.353802
57	H	-2.682189	5.540992	0.009394
58	H	-2.858451	4.321773	-1.259314



1.176

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(cyanomethyl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.176). To a solution of **1.148** (0.256 g, 0.515 mmol) in CH_3CN (4 mL) at 0 °C was added KO*t*Bu (0.57 mL, 1.0 M solution in THF) dropwise over 5 min. The reaction was quenched with sat. NH_4Cl (6 mL) and the resulting mixture was diluted with CH_2Cl_2 (60 mL). After separation, the organic phase was washed with brine (25 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (12-40% EtOAc:hexanes) afforded 0.118 g (55%) of **1.170**, 0.064 g

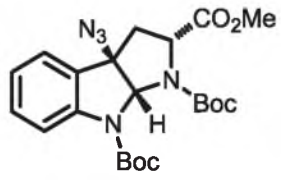
(25%) of **1.148**, and 0.036 g (15%) of **1.176**. **1.176**: white foam; R_f 0.11 (25% EtOAc:hexanes); $[\alpha]_D$ = −28.0 (*c* = 0.562, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (bs, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.15 (s, 1H), 4.62 (d, *J* = 7.5 Hz, 1H), 3.15 (s, 3H), 2.84 (d, *J* = 13.0 Hz, 1H), 2.70 (s, 2H), 2.55 (dd, *J* = 12.5, 9.5 Hz, 1H), 1.59 (s, 9H), 1.47 (bs, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 152.1, 142.8, 131.1, 129.9, 123.5, 123.3, 117.4, 116.1, 82.1, 81.2, 80.4, 59.4, 52.3, 52.0, 37.7, 28.3, 28.2, 26.3; IR (neat) 2978, 2251, 1712, 1604, 1481, 1393, 1367, 1332, 1272, 1159, 1067, 1025, 905, 858, 753, 737 cm^{-1}; LRMS (ESI) calcd for $C_{24}H_{31}N_3O_6Na$ *m/z* ($M+Na^+$) 480.2, found 480.2.



1.186

Preparation of (2*R*,3a*S*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.186). To a solution of cyclopropane **1.170** (0.029 g, 0.070 mmol) in THF (1.5 mL) at rt was added $NaBH_4$ (0.013 g, 0.34 mmol). After the reaction mixture was allowed to stir for 2 h, the reaction was quenched with H_2O (6 mL). The resulting mixture was diluted with CH_2Cl_2 (5 mL), separated, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (12-25% EtOAc:hexanes) afforded 0.011 g of **1.186** (75% yield) as a white foam. **1.186**: R_f 0.20 (20% EtOAc:hexanes); $[\alpha]_D$ = −3.0 (*c* = 0.172, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (broad, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H),

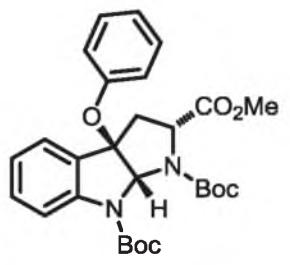
6.42 (d, J = 6.8 Hz, 1H), 4.57 (d, J = 8.4 Hz, 1H), 3.97 (dd, J = 6.8, 6.8 Hz, 1H), 3.14 (s, 3H), 2.60 (d, J = 13.2 Hz, 1H), 2.55-2.47 (m, 1H), 1.59 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 153.3, 152.4, 143.2, 131.6, 128.3, 123.9, 122.9, 117.0, 81.3, 80.6, 76.7, 59.3, 51.8, 44.7, 33.8, 29.6, 28.3, 28.3; IR (neat) 2978, 1716, 1604, 1482, 1458, 1396, 1366, 1258, 1163, 1112, 1048, 1018, 935, 900, 859, 753 cm^{-1}; LRMS (ESI) calcd for $C_{22}H_{30}N_2O_6Na$ *m/z* ($M+Na^+$) 441.2, found 441.2.



1.187

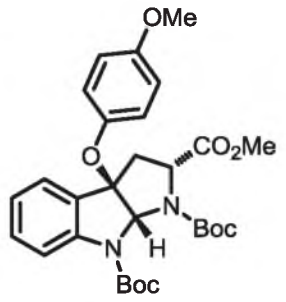
Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-azido-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.187). A mixture of cyclopropane **1.170** (0.088 g, 0.21 mmol), sodium azide (0.137 g, 2.10 mmol), and PPTS (0.053 g, 0.21 mmol) and DMF (1 mL) was stirred at rt for 3 h after which it was diluted with Et_2O (100 mL) and washed with water (3 x 10 mL). The organic layer was dried ($MgSO_4$) and concentrated. Flash chromatography (20% EtOAc:hexanes) afforded 0.070 g of **1.187** (72%) as a white foam. **1.187**: R_f 0.35 (20% EtOAc:hexanes); $[\alpha]_D$ = −104.1 (c = 0.593, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (bs, 1H), 7.35 (dt, J = 8.0, 1.2 Hz, 1H), 7.23 (dd, J = 7.6, 0.8 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.19 (s, 1H), 4.62 (d, J = 9.2 Hz, 1H), 3.15 (s, 3H), 2.82 (d, J = 12.8 Hz, 1H), 2.59 (dd, J = 12.9, 9.4 Hz, 1H), 1.58 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 153.0, 152.0, 143.8, 131.0, 127.9, 123.7, 123.6, 118.1, 82.1, 81.3, 80.9, 73.6, 59.1, 52.0, 37.8, 28.3, 28.2; IR (neat)

2978, 2102, 1719, 1604, 1479, 1393, 1367, 1335, 1255, 1162, 1090, 1065, 1018, 904, 857, 754 cm^{-1}; LRMS calcd for $C_{22}H_{29}N_5O_6Na$ m/z ($M+Na^+$) 482.2, found 482.2.



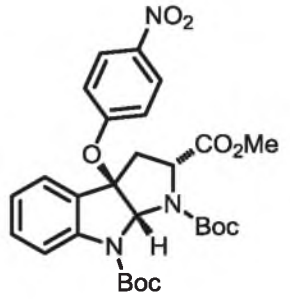
1.188

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-phenoxy-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.188). A solution of cyclopropane **1.170** (0.038 g, 0.090 mmol), phenol (0.043 g, 0.46 mmol), and DBU (0.014 mL, 0.090 mmol) in THF (1 mL) was stirred at rt for 6 h. Concentration and flash chromatography (5% EtOAc:hexanes) afforded 0.033 g of **1.188** (70%) as a white foam. **1.188**: R_f 0.40 (33% EtOAc:hexanes); $[\alpha]_D$= −72.8 (c = 0.325, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.28-7.23 (m, 2H), 7.11-7.06 (m, 2H), 7.01-6.93 (m, 2H), 6.72-6.60 (m, 2H), 6.41 (s, 1H), 4.64 (d, *J* = 8.8 Hz, 1H), 3.15 (s, 3H), 3.00 (dd, *J* = 12.6, 9.0, 1H), 2.94 (broad d, *J* = 11.7 Hz, 1 H), 1.49 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 154.6, 153.4, 151.8, 144.8, 130.8, 129.0, 128.9, 124.9, 124.2, 123.0, 122.1, 117.5, 91.3, 81.5, 81.0, 78.7, 58.7, 51.9, 39.6, 28.4, 28.2; IR (neat) 2976, 2930, 1760, 1705, 1591, 1489, 1479, 1389, 1365, 1253, 1153, 1067, 1012, 905, 858, 752 cm^{-1}; LRMS calcd for $C_{28}H_{34}N_2O_7Na$ m/z ($M+Na^+$) 533.2, found 533.2.



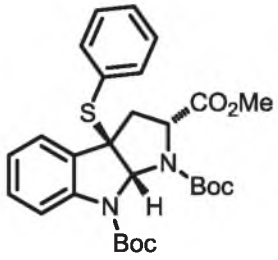
1.189

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(4-methoxyphenoxy)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.189). A solution of cyclopropane **1.170** (0.058 g, 0.14 mmol), *p*-methoxyphenol (0.087 g, 0.70 mmol) and DBU (0.021 mL, 0.14 mmol) in THF (1 mL) was stirred at rt for 10 h. Concentration and flash chromatography (7-20% EtOAc:hexanes) afforded 0.057 g of **1.189** (76%) as a white foam. **1.189**: R_f 0.48 (33% EtOAc:hexanes); $[\alpha]_D = -29.5$ (c = 0.273, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (bs, 1H), 7.28-7.24 (m, 2H), 7.01 (t, *J* = 7.7 Hz, 1H), 6.65-6.58 (m, 4H), 6.36 (s, 1H), 4.64 (d, *J* = 8.0 Hz, 1H), 3.66 (s, 3H), 3.13 (s, 3H), 3.00-2.90 (m, 2H), 1.44 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 156.1, 151.7, 151.7, 147.9, 145.0, 130.7, 129.1, 124.9, 123.5, 123.0, 117.8, 113.9, 91.3, 81.3, 81.0, 78.6, 58.6, 55.2, 51.8, 38.8, 28.4, 28.2; IR (neat) 2980, 2929, 2854, 1715, 1504, 1392, 1367, 1264, 1205, 1159, 1068, 1013, 902, 732, 702 cm^{-1}; LRMS calcd for $C_{29}H_{36}N_2O_8Na$ m/z ($M+Na^+$) 563.2, found 563.2



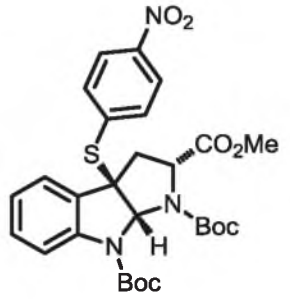
1.190

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(4-nitrophenoxy)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.190). A solution of cyclopropane **1.170** (0.042 g, 0.10 mmol), *p*-nitrophenol (0.070 g, 0.50 mmol) and DBU (0.018 mL, 0.11 mmol) in THF (1 mL) was stirred at rt for 48 h. Concentration and flash chromatography (7-20% EtOAc:hexanes) afforded 0.039 g of **1.190** (70%) as a white foam. **1.190**: R_f 0.44 (33% EtOAc:hexanes); $[\alpha]_D$= −96.4 (c = 0.452, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.96 (m, 2H), 7.59 (broad s, 1H), 7.31 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.77-6.73 (m, 2H), 6.45 (s, 1H), 4.76 (dd, *J* = 7.0, 2.7 Hz, 1H), 3.21 (s, 3H), 3.06-2.97 (m, 2H), 1.52 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 160.2, 153.1, 151.7, 144.5, 143.4, 131.5, 127.5, 125.1, 124.5, 123.6, 120.8, 117.3, 92.3, 82.1, 81.4, 78.4, 58.6, 52.1, 40.9, 28.3, 28.2; IR (neat) 2977, 2927, 1758, 1707, 1590, 1519, 1479, 1390, 1342, 1244, 1153, 1009, 910, 859, 751 cm^{-1}; LRMS calcd for $C_{28}H_{33}N_3O_9Na$ m/z ($M+Na^+$) 578.2, found 578.2.



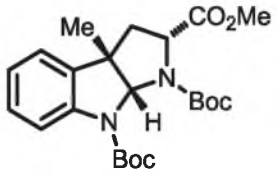
1.191

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(phenylthio)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.191). A solution of cyclopropane **1.170** (0.060 g, 0.14 mmol), thiophenol (0.080 mL, 0.73 mmol) and DBU (0.022 mL, 0.14 mmol) in THF (1 mL) was stirred at rt for 5 h. Concentration and flash chromatography (10% EtOAc:hexanes) afforded 0.064 g of **1.191** (84%) as a white foam. **1.191**: R_f 0.33 (20% EtOAc:hexanes); $[\alpha]_D = -16.8$ (c = 0.631, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (bs, 1H), 7.29-7.24 (m, 3H), 7.20-7.14 (m, 4H), 7.00-6.95 (m, 1H), 6.29 (s, 1H), 4.51 (d, *J* = 8.8 Hz, 1H), 3.10 (s, 3H), 2.86 (d, *J* = 13.0 Hz, 1H), 2.64 (dd, *J* = 12.8, 9.3 Hz, 1H), 1.53 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 152.7, 151.8, 143.4, 136.6, 131.3, 129.8, 129.4, 128.7, 124.0, 123.0, 117.2, 82.0, 81.3, 80.8, 61.8, 59.1, 51.8, 38.9, 28.3, 28.2; IR (neat) 2976, 2950, 2931, 1760, 1705, 1506, 1477, 1388, 1365, 1314, 1253, 1151, 1057, 1015, 913, 887, 856, 748 cm^{-1}; LRMS calcd for $C_{28}H_{34}N_2O_6SNa$ m/z ($M+Na^+$): 549.2, found 549.2.



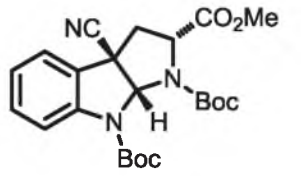
1.192

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-((4-nitrophenyl)thio)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.192). A solution of cyclopropane **1.170** (0.060 g, 0.14 mmol), *p*-nitrobenzenethiol (0.108 g, 0.700 mmol) and DBU (0.021 ml, 0.14 mmol) in THF (1 mL) was stirred at rt for 1 h. Concentration and flash chromatography (10% EtOAc:hexanes) afforded 0.064 g of **1.192** (80%) as a white foam. **1.192**: R_f 0.24 (20% EtOAc:hexanes); $[\alpha]_D = -41.2$ (c = 0.527, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.93 (m, 2H), 7.36-7.24 (m, 4H), 7.19 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.03 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.33 (s, 1H), 4.59 (d, *J* = 8.8 Hz, 1H), 3.12 (s, 3H), 2.95 (d, *J* = 12.8 Hz, 1H), 2.70 (dd, *J* = 12.8, 9.1 Hz, 1H), 1.45 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 152.7, 151.4, 148.1, 143.4, 138.5, 136.3, 130.5, 130.0, 124.0, 123.4, 123.3, 117.1, 82.4, 81.7, 81.1, 62.3, 59.0, 51.9, 39.3, 28.3, 28.1; IR (neat) 2977, 2931, 1706, 1521, 1477, 1388, 1342, 1254, 1152, 1057, 1014, 915, 887, 852, 744 cm^{-1}; LRMS calcd for $C_{28}H_{33}N_3O_8SNa$ m/z ($M+Na^+$) 594.2, found 594.2.



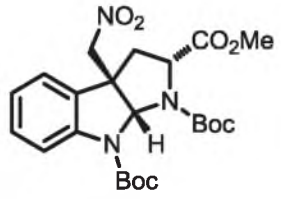
1.193

Preparation of (2*R*,3a*S*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-methyl-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.193). To a solution of cyclopropane **1.170** (0.125 g, 0.300 mmol) in CH_2Cl_2 (5 mL) at −40 °C was added $AlMe_3$ (0.30 mL of a 2.0 M solution in PhMe, 0.60 mmol). The reaction mixture was allowed to warm to 0 °C for 0.5 h at which time the reaction was quenched with 30% Rochelle Salt (2 mL). The resulting mixture was diluted with CH_2Cl_2 (60 mL) and the phases were separated. The organic phase was washed with brine (20 mL, dried ($MgSO_4$), and concentrated. Flash chromatography (12-15% EtOAc:hexanes) afforded 0.099 g of **1.193** (76% yield) as a white foam. **1.193**: R_f 0.33 (20% EtOAc:hexanes); $[\alpha]_D$ = −5.6 (*c* = 1.552, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (bs, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.97 (t, *J* = 7.8 Hz, 1H), 5.97 (s, 1H), 4.54 (d, *J* = 7.3 Hz, 1H), 3.13 (s, 3H), 2.66 (d, *J* = 12.7 Hz, 1H), 2.34 (dd, *J* = 12.7, 9.3 Hz, 1H), 1.59 (s, 9H), 1.47 (bs, 9H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 152.6, 152.6, 142.3, 136.0, 128.3, 123.1, 122.5, 117.3, 82.1, 81.5, 80.8, 59.8, 59.6, 51.8, 40.1, 28.3, 28.3, 24.5; IR (neat) 2977, 1758, 1713, 1603, 1481, 1455, 1395, 1367, 1257, 1167, 1107, 1016, 906, 860, 752 cm^{-1}; LRMS (ESI) calcd for $C_{23}H_{32}N_2O_6Na$ *m/z* ($M+Na^+$) 455.2, found 455.2.



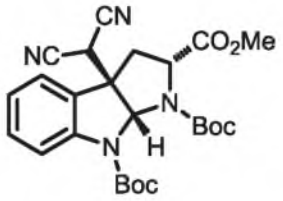
1.194

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-cyano-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.194). A mixture of cyclopropane **1.170** (0.045 g, 0.11 mmol), KCN (0.071 g, 1.090 mmol), 18-crown-6 (0.003 g, 0.01 mmol), PPTS (0.030 g, 0.12 mmol) and THF (1 mL) was stirred at rt for 3.5 h after which it was diluted with CH_2Cl_2 (8 mL), filtered, and concentrated. Flash chromatography (12-33% EtOAc:hexanes) afforded 0.034 g (70%) of **1.194** as a white foam. **1.194**: R_f 0.32 (33% EtOAc:hexanes); $[\alpha]_D = -3.7$ (*c* = 0.380, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (broad, 1H), 7.32 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.27 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.07 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.68 (s, 1H), 4.72 (d, *J* = 8.3 Hz, 1H), 3.18 (s, 3H), 3.18 (d, *J* = 12.7 Hz, 1H), 2.89 (dd, *J* = 13.2, 9.3 Hz, 1H), 1.60 (s, 9H), 1.48 (broad s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 152.4, 151.4, 142.8, 130.8, 126.4, 123.9, 123.8, 118.4, 117.5, 82.5, 81.9, 80.0, 59.0, 52.2, 47.1, 39.5, 28.2, 28.2; IR (neat) 2980, 2243, 1719, 1482, 1392, 1369, 1325, 1258, 1158, 1090, 1060, 1017, 907, 857, 756 cm^{-1}; LRMS (ESI) calcd for $C_{23}H_{30}N_3O_6$ *m/z* ($M+H^+$) 444.2, found 444.2.



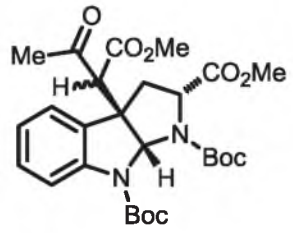
1.195

Preparation of (2*R*,3a*S*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(nitromethyl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.195). A solution of cyclopropane **1.170** (0.086 g, 0.21 mmol), DBU (0.063 mL, 0.42 mmol), and nitromethane (1 mL) in THF (4 mL) at rt was stirred for 6 h. The reaction mixture was diluted with CH_2Cl_2 (60 mL) and the reaction was quenched with 5% citric acid (25 mL). After separation, the organic phase was washed with brine (25 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (12-33% EtOAc:hexanes) afforded 0.050 g of **1.195** (50%) as a white foam. **1.195**: R_f 0.30 (33% EtOAc:hexanes); $[\alpha]_D = -20.2$ (*c* = 0.856, $CHCl_3$); ^{1}H NMR (~2:1 mix of rotamers, 500 MHz, $CDCl_3$) major rotamer δ 7.62 (bs, 1H), 7.32-7.26 (m, 1H), 7.08-7.04 (m, 1H), 7.04-6.98 (m, 1H), 6.41 (s, 1H), 4.63 (bs, 1H), 4.61 (d, *J* = 2.5 Hz, 2H), 3.14 (s, 3H), 2.84 (d, *J* = 13.0 Hz, 1H), 2.56 (dd, *J* = 13.0, 9.5 Hz, 1H), 1.59 (s, 9H), 1.46 (bs, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) mix of rotamers δ 171.5, 171.1, 152.5, 152.1, 143.4, 143.2, 131.8, 130.6, 130.6, 130.2, 129.0, 124.4, 123.6, 123.3, 123.2, 117.5, 84.5, 82.1, 81.9, 81.7, 81.6, 81.3, 79.2, 59.2, 54.1, 52.3, 52.0, 51.9, 39.4, 36.8, 28.3, 28.2, 28.2; IR (neat) 2979, 1722, 1604, 1556, 1481, 1395, 1368, 1335, 1257, 1160, 1017, 903, 858, 753, 737 cm^{-1}; LRMS (ESI) calcd for $C_{23}H_{31}N_3O_8Na$ *m/z* ($M+Na^+$) 500.2, found 500.2.



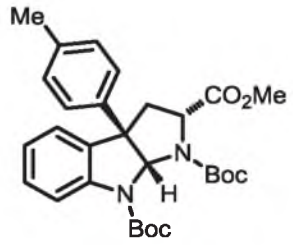
1.196

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(dicyanomethyl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.196). A solution of cyclopropane **1.170** (0.078 g, 0.19 mmol), malononitrile (0.062 g, 0.94 mmol), and DBU (0.032 mL, 0.21 mmol) in THF (2 mL) was stirred for 1 h at rt. The reaction mixture was passed through a plug of silica gel and concentrated. Flash chromatography (10% EtOAc:hexanes) afforded 0.055 g of **1.196** (60%) as a white foam. **1.196**: R_f 0.15 (33% EtOAc:hexanes); $[\alpha]_D = -15.3$ (c = 0.694, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (broad, 1H), 7.39-7.34 (m, 2H), 7.09 (t, J = 7.6 Hz, 1H), 6.33 (s, 1H), 4.65 (d, J = 8.1 Hz, 1H), 4.23 (s, 1H), 3.16 (s, 3H), 2.94 (d, J = 12.8 Hz, 1H), 2.72-7.67 (m, 1H), 1.57 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.7, 151.8, 143.7, 131.2, 127.1, 123.9, 118.4, 110.5, 110.2, 82.6, 81.8, 79.3, 59.1, 55.3, 52.1, 36.3, 30.6, 28.3, 28.2; IR (neat) 2981, 2891, 1723, 1604, 1481, 1394, 1369, 1331, 1274, 1161, 1093, 1072, 1020, 916, 893, 856, 757 cm^{-1}; LRMS (ESI) calcd for $C_{25}H_{30}N_4O_6Na$ m/z ($M+Na^+$) 505.2, found 505.2.



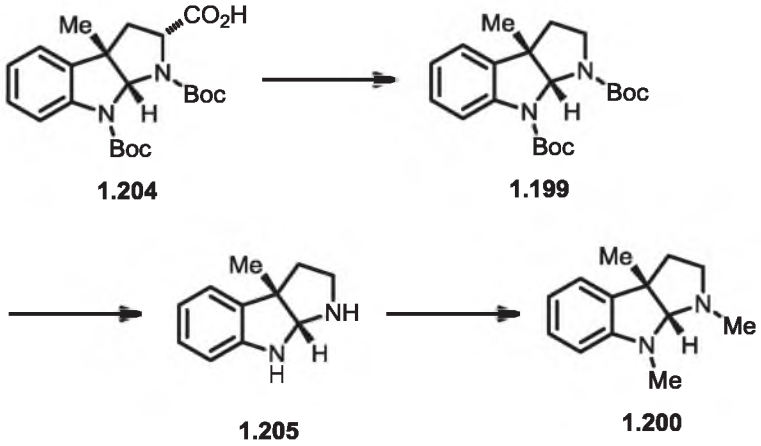
1.197

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(1-methoxy-1,3-dioxobutan-2-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.197). A solution of cyclopropane **1.170** (0.833 g, 2.01 mmol), methyl acetoacetate (0.43 mL, 4.0 mmol), and DBU (0.30 mL, 2.0 mmol) in THF (10 mL) was stirred for 12 h at rt. The reaction mixture was passed through a plug of silica gel and concentrated. Flash chromatography (15-40% EtOAc:hexanes) afforded 0.799 g of **1.197** (75%) as a white foam. **1.197**: R_f 0.09 (20% EtOAc:hexanes); $[\alpha]_D = -20.4$ (c = 0.812, $CHCl_3$); ^1H NMR (mixture of isomers and tautomers, 500 MHz, $CDCl_3$) δ 7.50 (bs, 3.2H), 7.29-7.24 (m, 2.3H), 7.21 (t, J = 7.3 Hz, 2.3H), 7.11 (t, J = 6.8 Hz, 2.3H), 7.02-7.07 (m, 1.1H), 6.96 (t, J = 6.8 Hz, 1.3H), 6.94 (t, J = 6.8 Hz, 1.3H), 6.46 (s, 1H), 6.41 (s, 1H), 6.29 (bs, 0.4H), 6.25 (s, 0.4H), 4.60 (bs, 2.3H), 3.94- 3.76 (m, 4.3H), 3.72 (s, 3.5H), 3.70 (s, 3.7H), 3.67-3.62 (m, 4.2H), 3.13 (s, 6.7H), 2.94 (dd, J = 6.8, 12.7 Hz, 1H), 2.86-2.76 (m, 4.7H), 2.52 (dd, J = 11.7, 11.7 Hz, 1H), 2.15 (s, 1.3H), 2.08 (s, 6.2H), 2.01 (s, 1.4H), 1.59 (s, 31H), 1.46 (s, 31H); ^{13}C NMR (mixture of isomers and tautomers, 125 MHz, $CDCl_3$) δ 172.0, 167.9, 167.7, 152.4, 143.5, 143.4, 142.3, 131.8, 129.7, 124.9, 124.4, 124.3, 123.3, 117.9, 81.9, 81.7, 80.0, 79.4, 63.0, 62.8, 59.4, 59.3, 53.0, 52.9, 52.4, 52.1, 37.0, 36.1, 31.6, 31.4, 28.5; IR (neat) 2979, 1722, 1603, 1481, 1455, 1435, 1394, 1367, 1328, 1267, 1201, 1159, 1018, 906, 859, 753, 737 cm^{-1}; LRMS (ESI) calcd for $C_{27}H_{37}N_2O_9Na$ *m/z* ($M+H^+$) 533.2, found 533.2.



1.198

Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(*p*-tolyl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.198). To a suspension of CuCN (0.197 g, 2.19 mmol) in THF (3.5 mL) at −78 °C was added *p*-tolylmagnesium bromide (3.66 mL of a 0.5 M solution in Et_2O, 1.83 mmol). The reaction mixture was allowed to warm to 0 °C for 20 min. and was then cooled back to −78 °C. To the resulting solution was added a solution of cyclopropane **1.170** (0.152 g, 0.366 mmol) in THF (3.5 mL) dropwise. The resulting reaction mixture was allowed to stir for 15 min. at which time the reaction was quenched with sat. NH_4Cl (6 mL) and then diluted with CH_2Cl_2 (150 mL). After separation the organic phase was washed sequentially with water (25 mL) and brine (25 mL), and then dried ($MgSO_4$), and concentrated. Flash chromatography (10-15% EtOAc:hexanes) afforded 0.130 g (70%) of **1.198** as a white foam. **1.198**: R_f 0.26 (15% EtOAc:hexanes); $[\alpha]_D$ = −39.2 (*c* = 0.186, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (bs, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.11-7.05 (m, 5H), 6.96 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.42 (s, 1H), 4.70 (bs, 1H), 3.16 (s, 3H), 3.08-3.02 (m, 1H), 2.86 (dd, *J* = 12.8, 9.0 Hz, 1H), 2.28 (s, 3H), 1.57 (s, 9H), 1.48 (bs, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 152.4, 152.4, 142.6, 139.2, 136.9, 129.5, 128.6, 125.3, 124.0, 123.4, 118.4, 117.0, 82.6, 82.6, 81.5, 59.5, 51.9, 40.1, 38.6, 28.4, 28.3, 20.9; IR (neat) 2977, 1758, 1712, 1601, 1515, 1480, 1393, 1367, 1323, 1257, 1158, 1017, 928, 859, 752 cm^{-1}; LRMS (ESI) calcd for $C_{29}H_{36}N_2O_6Na$ *m/z* ($M+Na^+$) 531.2, found 531.2.



Preparation of (3a*S*,8a*R*)-1,3a,8-trimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (1.200). A mixture of **1.193** (0.220 g, 0.517 mmol), NaOH (0.083 g, 2.1 mmol), and THF:MeOH:H_2O (10:5:2 mL) was stirred at 40 °C for 4 h. The mixture was concentrated and the resulting residue was diluted with EtOAc (60 mL) and 5% aq. citric acid (25 mL). After separation, the organic phase was washed with H_2O (25 mL), brine (25 mL), dried ($MgSO_4$) and concentrated to give acid **1.204** which was used without further purification.

To an aluminum foil covered flask containing a mixture of acid **1.204** (0.517 mmol), EDC·HCl (0.119 g, 0.620 mmol), and 2-mercaptopyridine-N-oxide (0.078 g, 0.62 mmol) in CH_2Cl_2 (6 mL) at rt was added Et_3N (0.16 mL, 1.1 mmol). After the reaction mixture had stirred for 1.5 h, *t*-BuSH (0.29 mL, 2.6 mmol), the aluminum foil was removed and the resulting mixture was irradiated under a sun lamp (250 W) for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (60 mL) and the organic phase was sequentially washed with 5% aq. citric acid (25 mL), 5% NaOH (25 mL), H_2O (25 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$), and concentrated. Flash chromatography (5% EtOAc:hexanes) afforded 0.101 g of pyrroloindoline **1.199** (52% yield) as a pale yellow

oil.

To a solution of **1.199** (0.410 g, 1.10 mmol) in CH_3CN (6 mL) at 0 °C was added TMSI (0.75 mL, 5.5 mmol). After the reaction mixture had stirred for 1 h, the reaction was quenched with sat. $NaHCO_3$ (6 mL) and the resulting mixture was diluted with CH_2Cl_2 (60 mL). The phases were separated and the organic phase was washed with sat. $NaHCO_3$ (25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated to afford bis-amine **1.205** which was used in the subsequent reaction without additional purification.

To a solution of bis-amine **1.205** in EtOAc:MeOH (10 mL, 2:1) at rt was added 37% aq. formalin (8 mL). After stirring for 0.5 h, 10% Pd/C (0.2 g, 50% water content) was added to the reaction mixture. The mixture was then stirred for 12 h under H_2 (1 atm.) After 12 h, additional 37% aq. formalin (4 mL) and 10% Pd/C (0.1 g, 50% water content) were added and the reaction mixture was stirred for an additional 8 h. The mixture was filtered through a plug of celite and the celite was rinsed with EtOAc:MeOH (10 mL, 1:1). The filtrate was concentrated and the resulting residue was purified by prep TLC (CH_2Cl_2:MeOH:Et_3N, 100:2:0.5) to afford 0.131 g (59%, 2 steps) of bis-methylamine **1.200** as a yellow oil. **1.200**: R_f 0.22 (5% MeOH:CH_2Cl_2); $[\alpha]_D = -72.2$ (c = 0.416 , $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.3 Hz, 1H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.42 (d, *J* = 7.8 Hz, 1H), 4.12 (s, 1H), 2.95 (s, 3H), 2.60-2.75 (m, 2H), 2.56 (s, 3H), 1.95-2.00 (m, 2H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 136.6, 127.7, 122.2, 117.5, 106.5, 97.5, 53.2, 52.6, 40.8, 38.4, 36.5, 27.3; IR (neat) 3360, 3049, 2957, 2928, 2864, 2792, 1680, 1606, 1492, 1374, 1299, 1255, 1124, 957, 896 cm^{-1}; LRMS calcd for $C_{13}H_{19}N_2$ m/z ($M+H^+$) 203.1, found 203.1.

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CHAPTER 2

TOTAL SYNTHESES OF KAPAKAHINES E and F

Introduction

Kapakahines A-G are a family of cyclic peptide natural products isolated from the marine sponge *Cribrochalina olemda* by Nakao, Scheuer, and co-workers (Figure 2.1).[1] Initial cytotoxicity testing of the natural isolates against P388 murine leukemia cells showed that the most active members were kapakahines A, B, C, and E with *in vitro* IC_{50} values of 5.1, 5.9, 4.7, 5.0 μM, respectively. Additional biological testing acquired by Baran and co-workers showed that synthetic kapakahine B displayed moderate activity against the breast cancer cell line DU4475 (IC_{50} value of 11.7 μM), however, synthetic kapakahines B and F did not show significant toxicity against the NCI 60-cell line.[2]

Structurally, the kapakahines are unique as they contain a C(3)-N(1′) heterodimeric linkage between two tryptophan residues and a tetracyclic framework containing an α-carboline and strained imidazolone (Figure 2.1). The sensitivity of the imidazolone ring toward nucleophiles in this type of framework is well-documented (see **2.8** to **2.9**, Figure 2.1).[3,4] Elucidation of the structures of the Kapakahines by Nakao, Scheuer, and co-workers was accomplished using a combination of degradation experiments with extensive NMR and FAB MS/MS. The structures of kapakahine F and B were unambiguously confirmed through total synthesis by Baran and coworkers in 2009 (vide

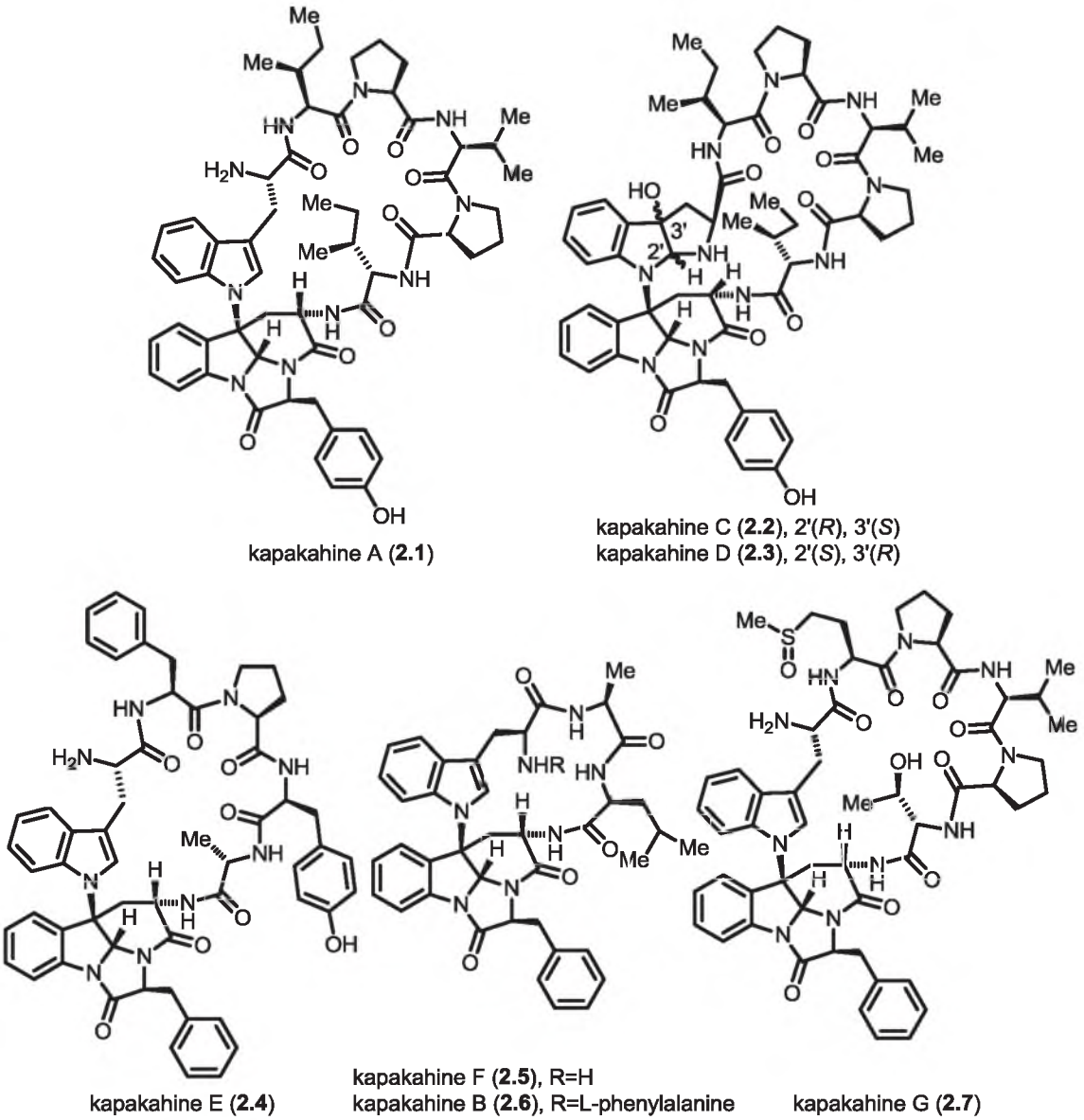


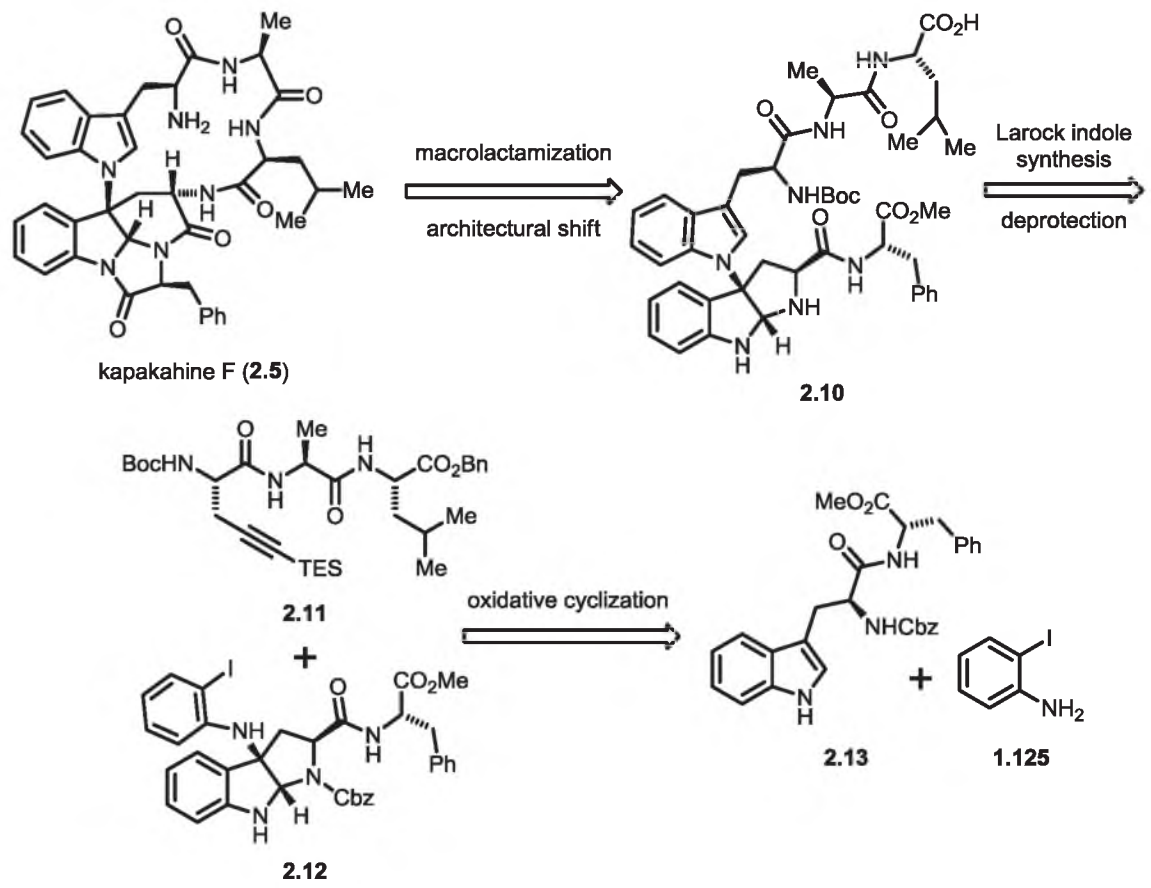
Figure 2.1. The Kapakahines and Their Strained Architecture

infra).[2,5]

Previous Work

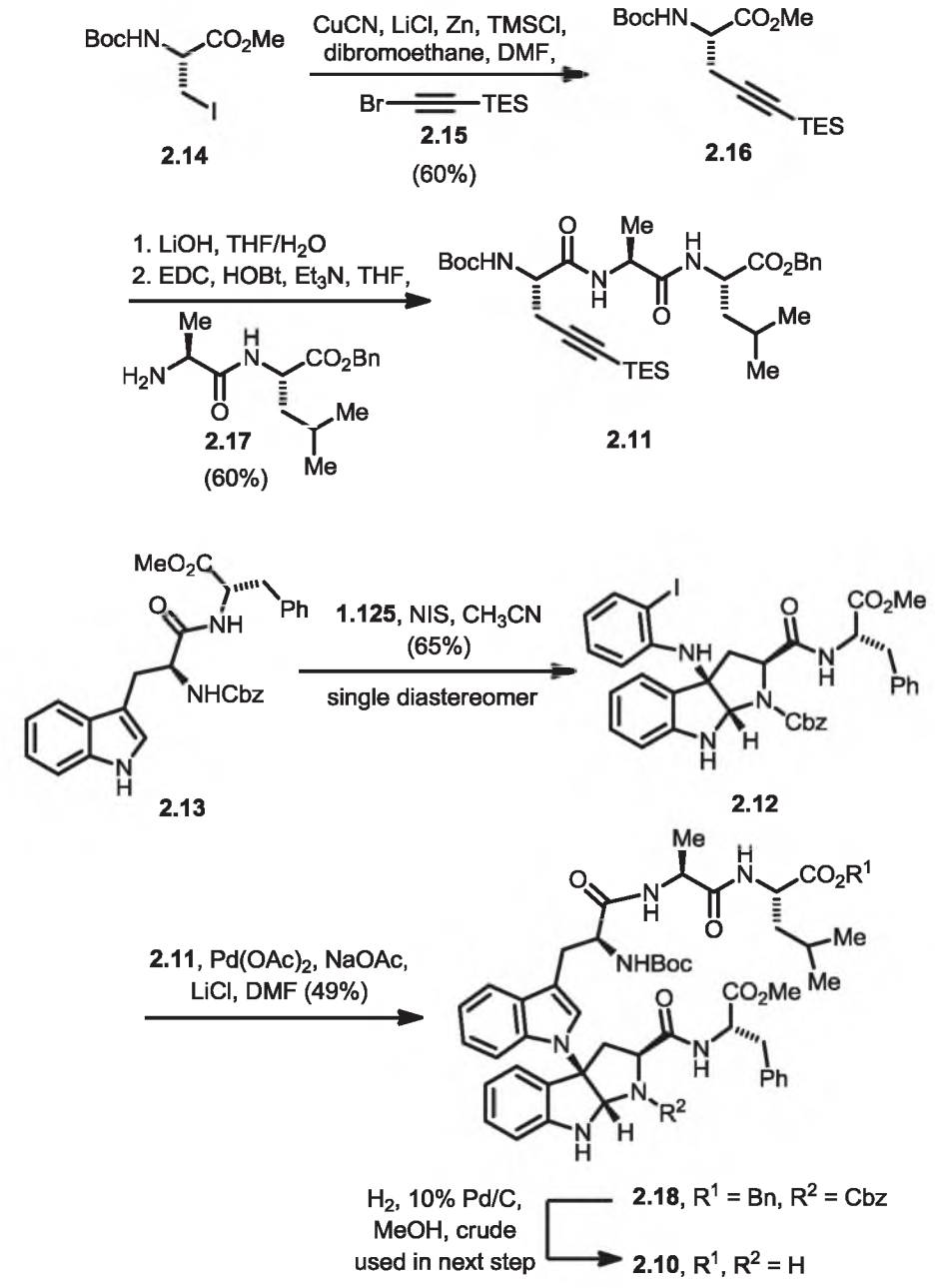
The methodology for Baran's construction of the C(3)-N(1′) bond of heterodimeric indolines was introduced in Chapter 1 (Scheme 1.16) and was utilized in their total synthesis of (±)-psychotrimine. They brilliantly adapted this work for their completion of the total syntheses of kapakahines F and B.[2,5] From the retrosynthesis it is seen that the success relied on a late-stage architectural shift from pyrroloindoline **2.10** to a macrocyclic α-carboline before conversion to kapakahine F (Scheme 2.1). The precursor **2.10** comes from a Larock indole synthesis between alkyne **2.11** and pyrroloindoline **2.12**, which in turn comes from a diastereoselective oxidative cyclization between tryptophan **2.13** and 2-iodoaniline.

Baran's synthesis began with the synthesis of Larock indole synthesis coupling partner **2.11** (Scheme 2.2). This tripeptide was completed by coupling TES protected bromoalkyne **2.15** with serine-derived iodide **2.14** to form alkyne **2.16**. Hydrolysis of the ester and peptide coupling with dipeptide **2.17** then provided tripeptide **2.11**. The other Larock indole synthesis coupling partner **2.12** was formed through an oxidative cycloaddition of 2-iodoaniline, activated with *N*-iodosuccinimide, on tryptophan **2.13** providing iodo-aniline **2.12** as a single diastereomer. The Larock indole synthesis performed smoothly to afford amino acid **2.10** after hydrogenolysis of the benzyl and Cbz protecting groups. The amino acid **2.10** was then ready to undergo the crucial rearrangment to the α-carboline.

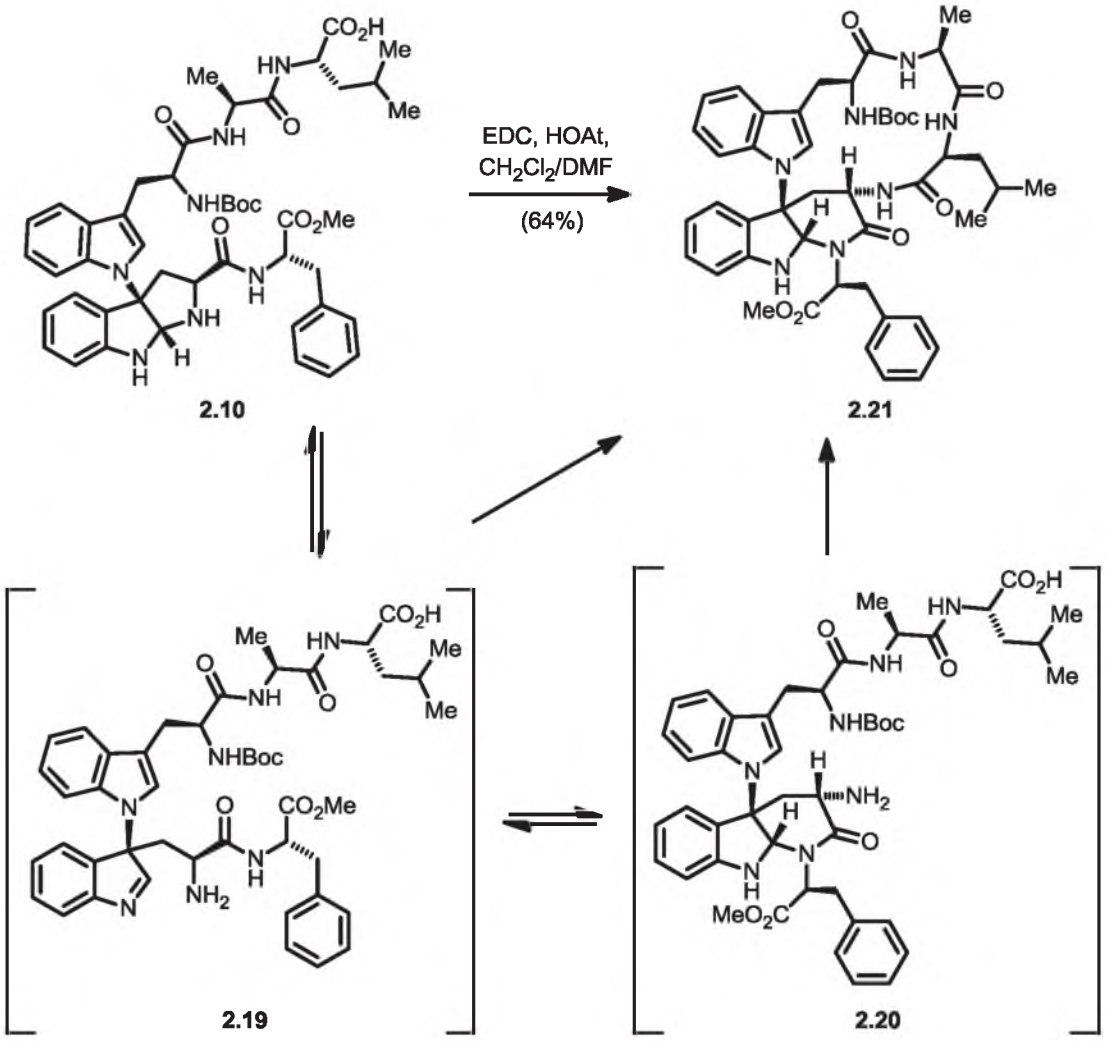


Scheme 2.1. Baran's Retrosynthesis of Kapakahine F

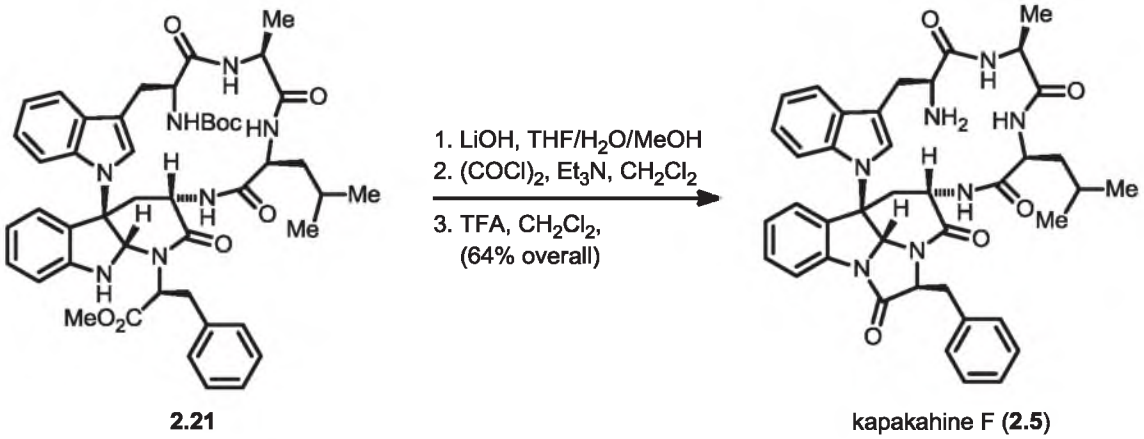
After considerable experimentation they found that using non-basic peptide coupling conditions could yield the desired α-carboline macrocycle **2.21** in good yield (Scheme 2.3). They proposed a mechanism that involved a rapid equilibrium between **2.10** and theoretical intermediates **2.19** and/or **2.20**. This allowed the starting material to be converted to the desired α-carboline macrocycle versus the pyrroloindoline macrocycle (i.e. Curtin-Hammett Principle).[7] With the desired α-carboline macrocycle **2.21** in hand, imidazolone incorporation and deprotection provided kapakahine F in 12 steps from L-serine. Kapakahine F was converted into kapakahine B in 2 steps through peptide coupling and deprotection (Scheme 2.4).



Scheme 2.2. Baran's Synthesis of Macrocyclization Precursor **2.10**



Scheme 2.3. Baran's Pyrroloindoline to α-Carboline Rearrangement



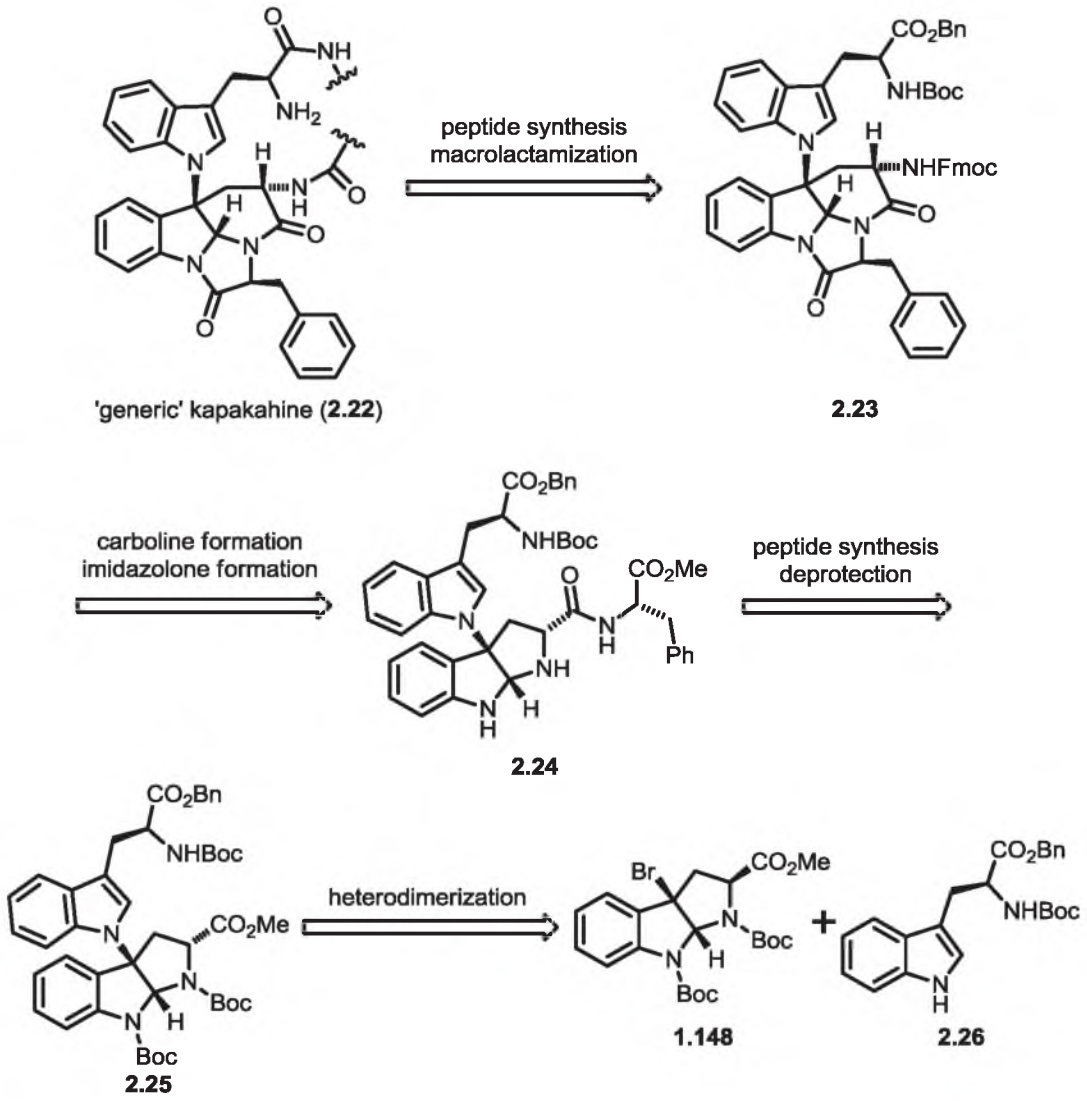
Scheme 2.4. Baran's Total Synthesis of Kapakahine F

Retrosynthesis

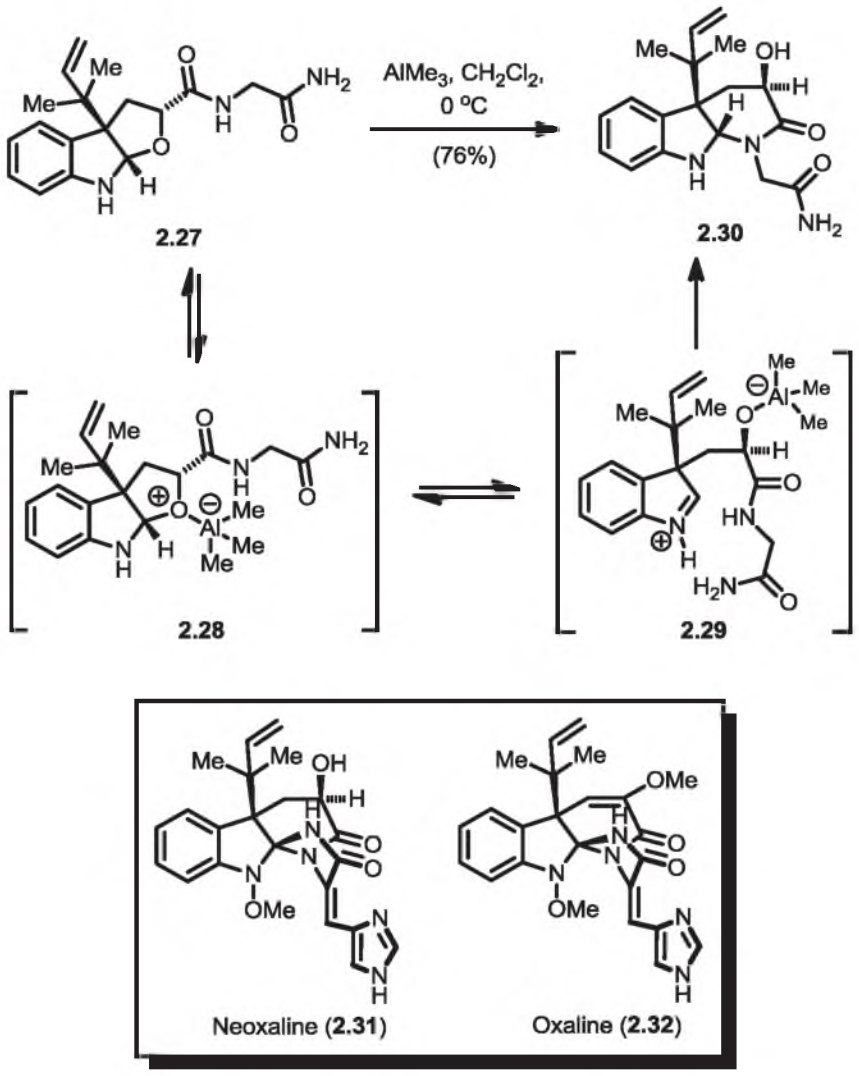
Our group initially chose Kapakahine E and B as targets because of their promising biological activities as well as the fact that a convergent synthesis could be envisioned to complete both natural products and analogs from the common bis-tryptophan heterodimer **2.23** (Scheme 2.5).[9] The proposed retrosynthesis began with the generation of 'generic' kapakahine macrocycle **2.22** from bis-tryptophan heterodimer **2.23** through peptide manipulation and lewis acid induced rearrangement to provide the macrolactam. The heterodimer **2.23** in turn could come from a pyrroloindoline to α-carboline rearrangement of **2.24** followed by concomitant imidazolone formation. This differs from Baran's proposal in that macrolactamization does not occur concurrently with, and is not required for, α-carboline synthesis. Finally, heterodimer **2.24** could come from peptide coupling and protecting group removal following our heterodimerization reaction as previously described in Chapter 1.

Pyrroloindoline to α-Carboline Rearrangement

At the time of commencement of this work, the only precedent on the rearrangement of a pyrroloindoline like architecture into an α-carboline had been published by Ōmura and coworkers in their synthesis of the neoxaline/oxaline core (Scheme 2.6).[8] The mechanism they proposed for this transformation involved lewis acid coordination to the oxygen of the furan in furanoindoline **2.28** followed by ring opening to the iminium ion **2.29** and then ring closing to the more thermodynamically stable α-carboline **2.30**. Further oxidation of the substrate allowed ring closure of the primary amide.



Scheme 2.5. Retrosynthesis



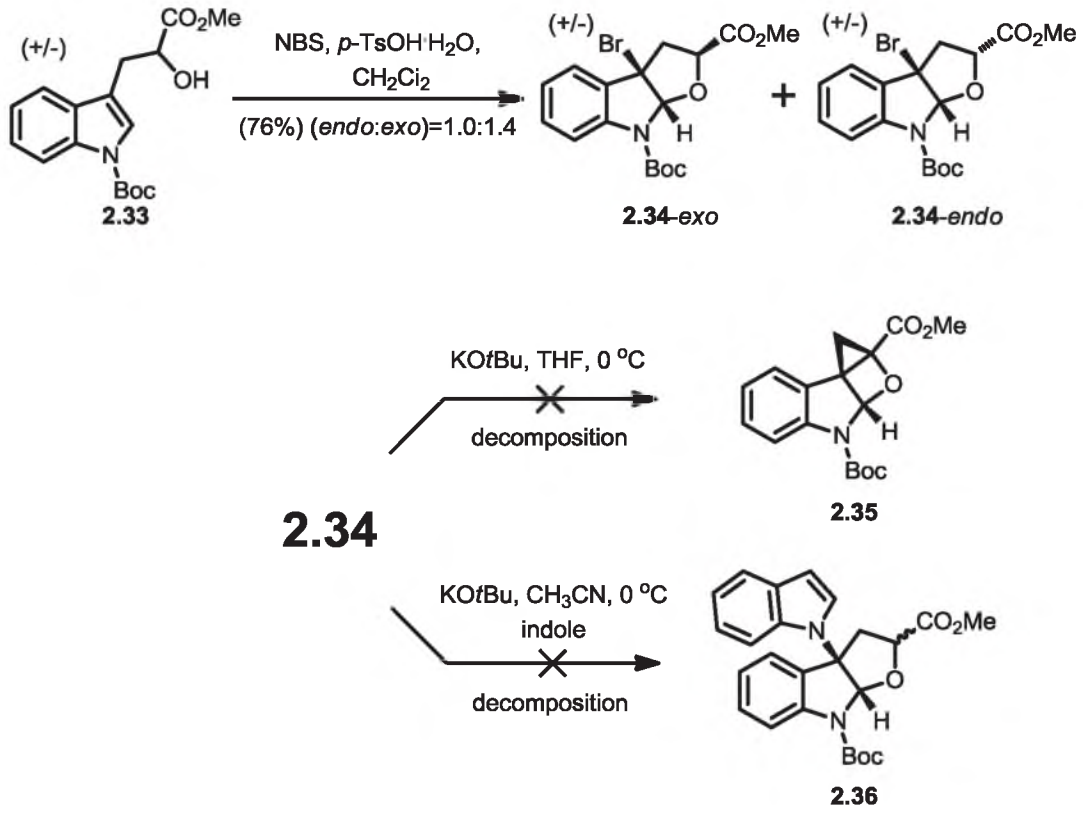
Scheme 2.6. Ōmura's α-Carboline Synthesis

Given the similarity of Ōmura and coworkers' furanoindoline to α-carboline transformation to our desired pyrroloindoline to α-carboline transformation, and the fact that no precedent existed at the time for the pyrroloindoline to α-carboline transformation, we decided to synthesize bromofuranoindoline **2.34** as an analog to bromopyrroloindoline **1.148** and attempt to engage it in the heterodimerization reaction as well as cyclopropyloxetindoline (**2.35**) formation (Scheme 2.7). Bromofuranoindolines **2.34**-*exo* and **2.34**-*endo* were synthesized from known indole lactic acid derivative **2.33** by cyclization with NBS and acid catalyst.[8]

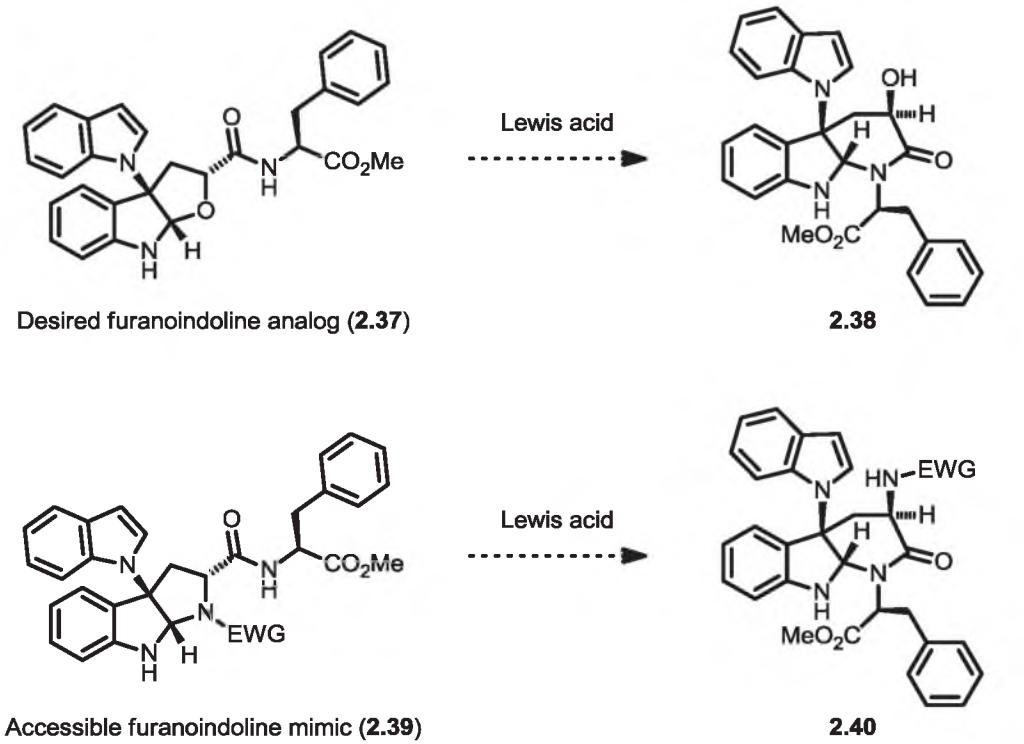
Though a tedious separation of the isomers is possible at this stage, **2.34** was used directly in the next step in part due to the mechanistic proposal that either isomer should be a substrate for the formation of **2.35** and **2.36**. Unfortunately, the conditions that were successful for **1.148** only led to decomposition of **2.34** (Scheme 2.7). In this case, the mechanism by which bromofuranoindoline **2.34** decomposes is still unclear and it is not known whether or not cyclopropyloxetindoline **2.35** is produced in the process of decomposition.[9]

In light of our results with **2.34**, we reexamined bromopyrroloindoline **1.148** as a starting point in the total synthesis. We believed that placing an electron-withdrawing group on the pyrrolo-nitrogen would allow it to act as good leaving group in the same fashion as the furan oxygen in Ōmura and coworker's furanoindoline to α-carboline transformation (Scheme 2.8).[10]

With this hypothesis, we synthesized furanoindoline mimic **2.42** as a model substrate to test the feasibility of the pyrroloindoline to α-carboline transformation (Scheme 2.9). The heterodimerization reaction was performed using indole as the nucleophile to give a



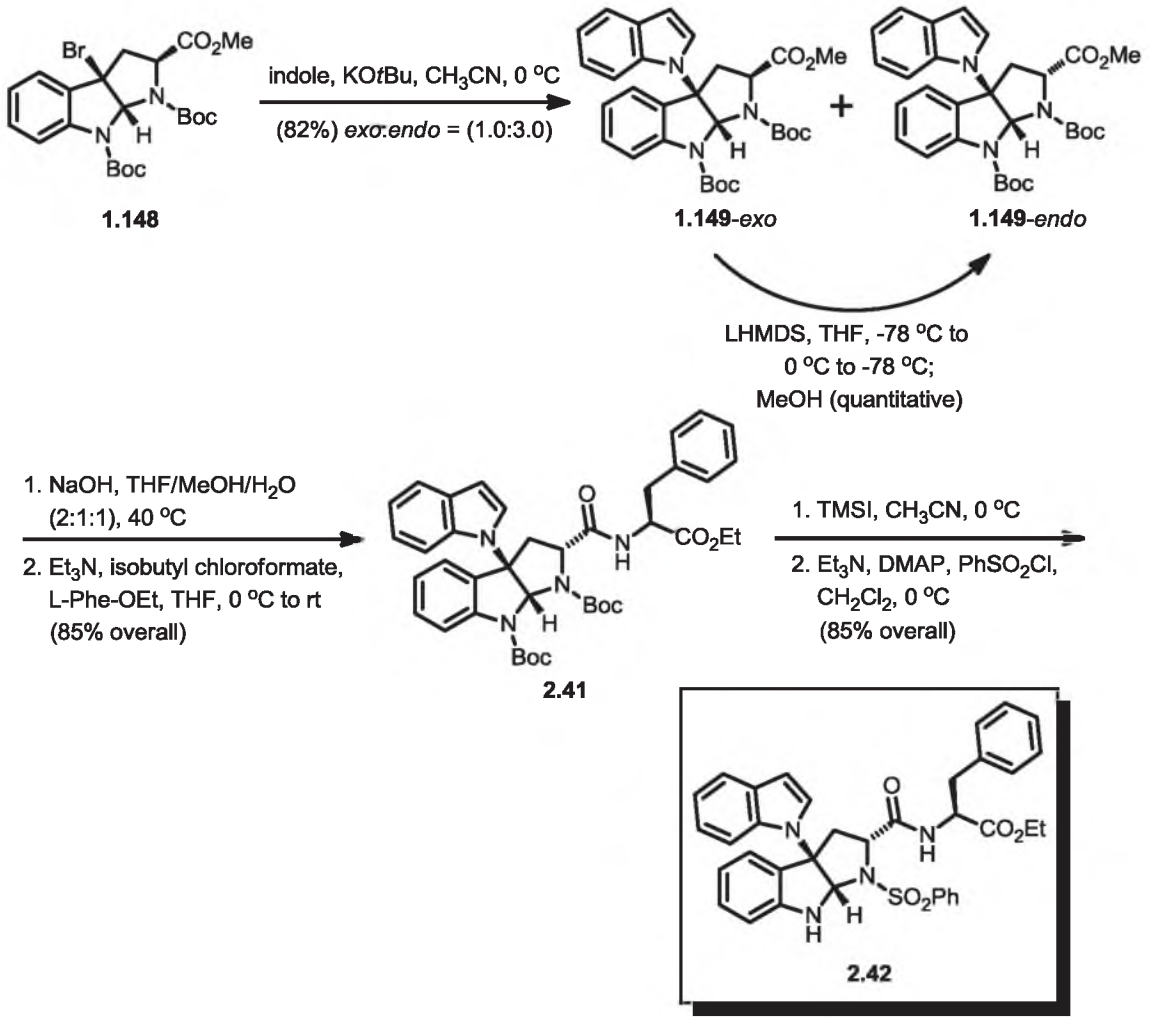
Scheme 2.7. Synthesis of **2.34** and Attempted Heterodimerization



Scheme 2.8. Furanoindoline Mimic for α-Carboline Synthesis

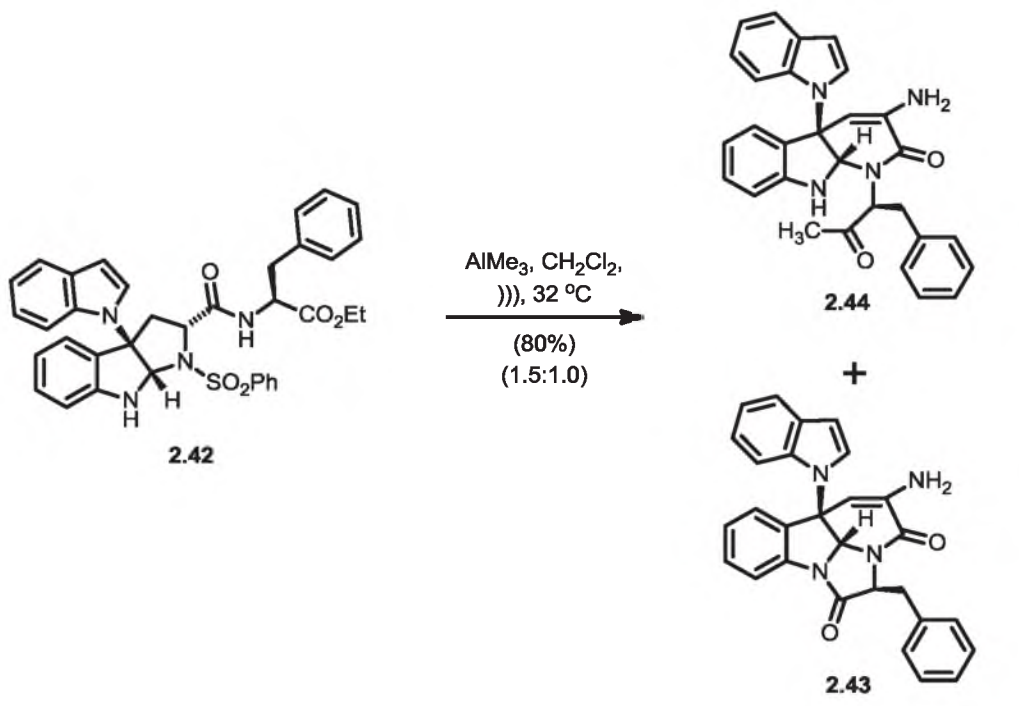
separable mixture of *endo* and *exo* isomers (**1.149**-*endo* and **1.149**-*exo*). After separation and conversion of isomer **1.149**-*exo* into isomer **1.149**-*endo*, the methyl ester was hydrolyzed and coupled with L-phenylalanine ethyl ester.[18] The Boc-protecting groups were removed using TMSI and CH_3CN and the pyrrolo-nitrogen was selectively protected with $PhSO_2Cl$ to give heterodimer **2.42** (Scheme 2.9).

Once the desired furanoindoline mimic **2.42** was in hand, the rearrangement was attempted using Ōmura and coworker's conditions. It was found that trimethylaluminum could elicit the expected α-carboline formation with the additional effect of inducing imidazolone formation by way of condensation between the aniline nitrogen and the pendant ester (Scheme 2.10).



Scheme 2.9. Synthesis of Heterodimer **2.42** for Rearrangement

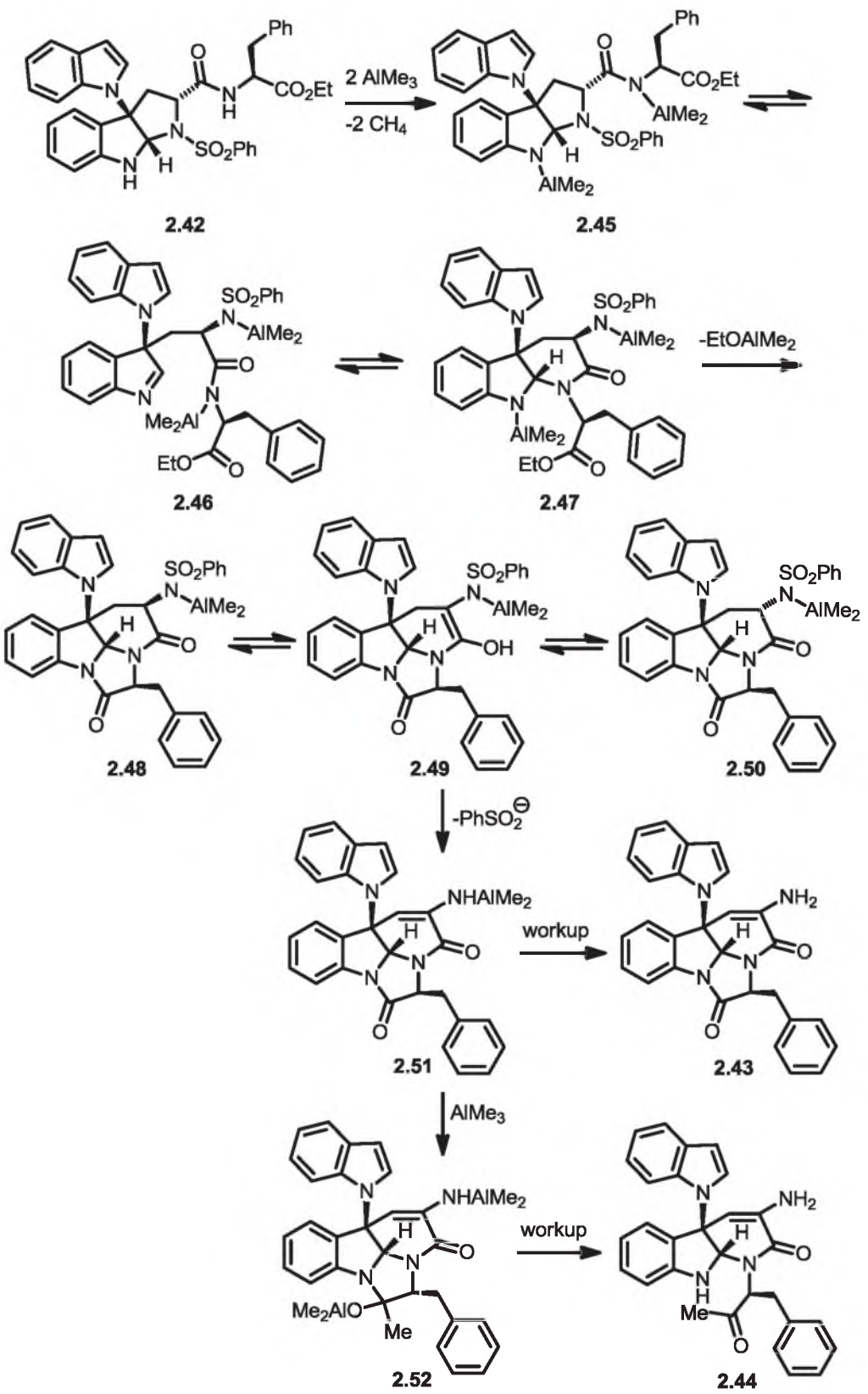
Under mild conditions (0 °C to rt) an excess of trimethylaluminum (10 eq.) appeared to give a complex mixture of compounds including starting material. Under more forcing conditions (0 °C to rt to 32 °C, sonication) an excess of trimethylaluminum (7 eq.) not only elicited tetracycle formation, but also elimination of sulfinate from the sulfonamide to give conjugated enamines **2.43** and **2.44** as an inseparable mixture in 80% yield (Scheme 2.10).[15d,e] The rearrangement of **2.42** to **2.43** and **2.44** proved to be quite sensitive to even seemingly insignificant changes in the reaction protocol and gave highly



Scheme 2.10. Rearrangement Results for **2.42**

variable ratios of **2.43**:**2.44** (0.5-1.5:1.0). Production of ketone **2.44** is thought to proceed by reaction of the strained imidazolone with excess trimethylaluminum. Numerous attempts to circumvent formation of **2.44** by using different lewis acids ($BF_3 \cdot OMe_2$, Et_3Al, Me_2AlCl, $MeAlCl_2$, $Sc(OTf)_3$, $Yb(OTf)_3$) and/or electron-withdrawing groups (triflyl, *p*-nosyl, dimethylsulfamoyl, carbobenzyloxy, *tert*-butylcarbonyl) on the pyrrolo-nitrogen were unsuccessful and only resulted in lower yields or sluggish reactivity.

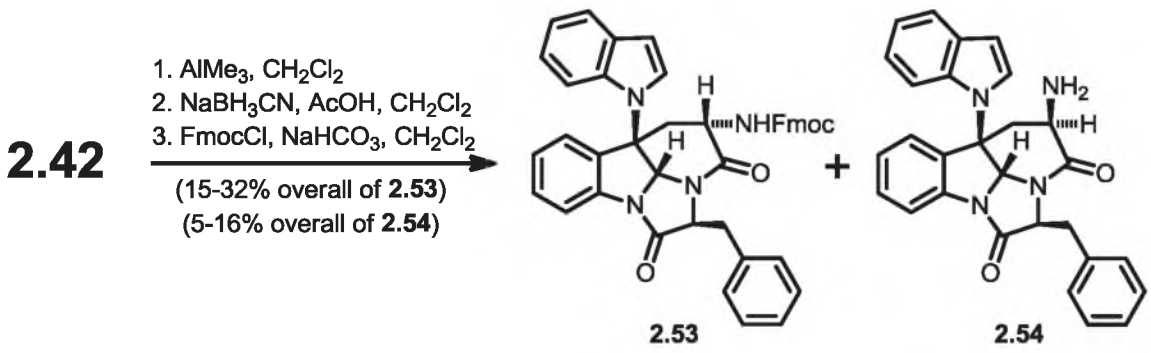
We proposed that $AlMe_3$ induced a reversible conversion of pyrroloindoline into α-carboline but that imidazolone formation was irreversible (Scheme 2.11). We proposed that after imidazolone formation, elimination of sulfinate from **2.48** and/or **2.50** through enol **2.49** produced enamine **2.51**. We then proposed that enamine **2.51** reacts with $AlMe_3$ giving a mixture of **2.43** and **2.44**.



Scheme 2.11. Proposed Mechanism for Rearrangement of **2.42**

Elimination of the sulfinate was thought to be an advantageous event because it solved the problem of removing the sulfonyl group later in the synthesis. In the absence of the elimination the stereochemistry at the ester would be epimeric for the kapakahines and we believed that reduction of the resulting enamine could be accomplished stereoselectively using substrate control to give the desired stereoisomer. In the event, a variety of reducing conditions were explored ($NaBH_3CN$/AcOH, $NaBH(OAc)_3$/AcOH, Et_3SiH/TFA, H_2/Pd/C, Al/Hg/AcOH, Zn/AcOH) and it was found that $NaBH_3CN$/AcOH was most effective (Scheme 2.12).[11] This gave the desired isomer as the major product, however, the overall yield remained low (15-33% yield from **2.42** for the desired isomer after introduction of the protecting group) and the selectivity could not be improved beyond 2:1 for the desired isomer.[19] The undesired isomer **2.54** was isolated after this capricious three step sequence in 5-16% yield and was found to be resistant to protection under the conditions that were effective for the protection of the desired isomer. The relatively low selectivity for the reduction can be explained due to the competing steric hindrance of the Bürgi-Dunitz trajectory from either face of the transient iminium ion (Figure 2.2).[12]

With this promising model study in hand, a direct introduction of a tryptophan derivative in place of indole was examined (Scheme 2.13). Tryptophan derivative **2.56** was designed and used due to stability reasons (tryptophan derivative **1.154** performed poorly in the heterodimerization reaction) and the orthogonal functionality it imparted to the product **2.57**. Thus, L-tryptophan was reduced with LAH and protected as a TIPS ether and the amine converted to an azide to afford **2.56**. Heterodimerization with the bromide provided **2.57** in good yield. Peptide synthesis and protecting group



Scheme 2.12. Rearrangement, Reduction, and Protection from **2.42**

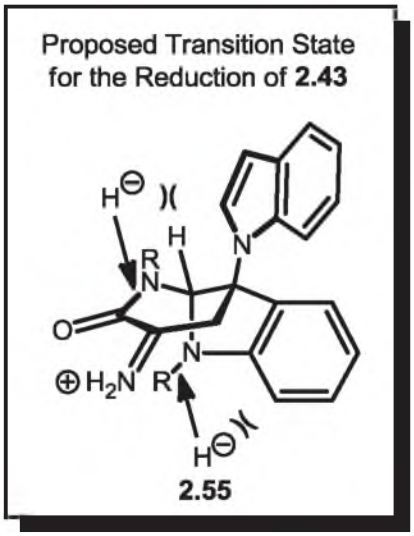
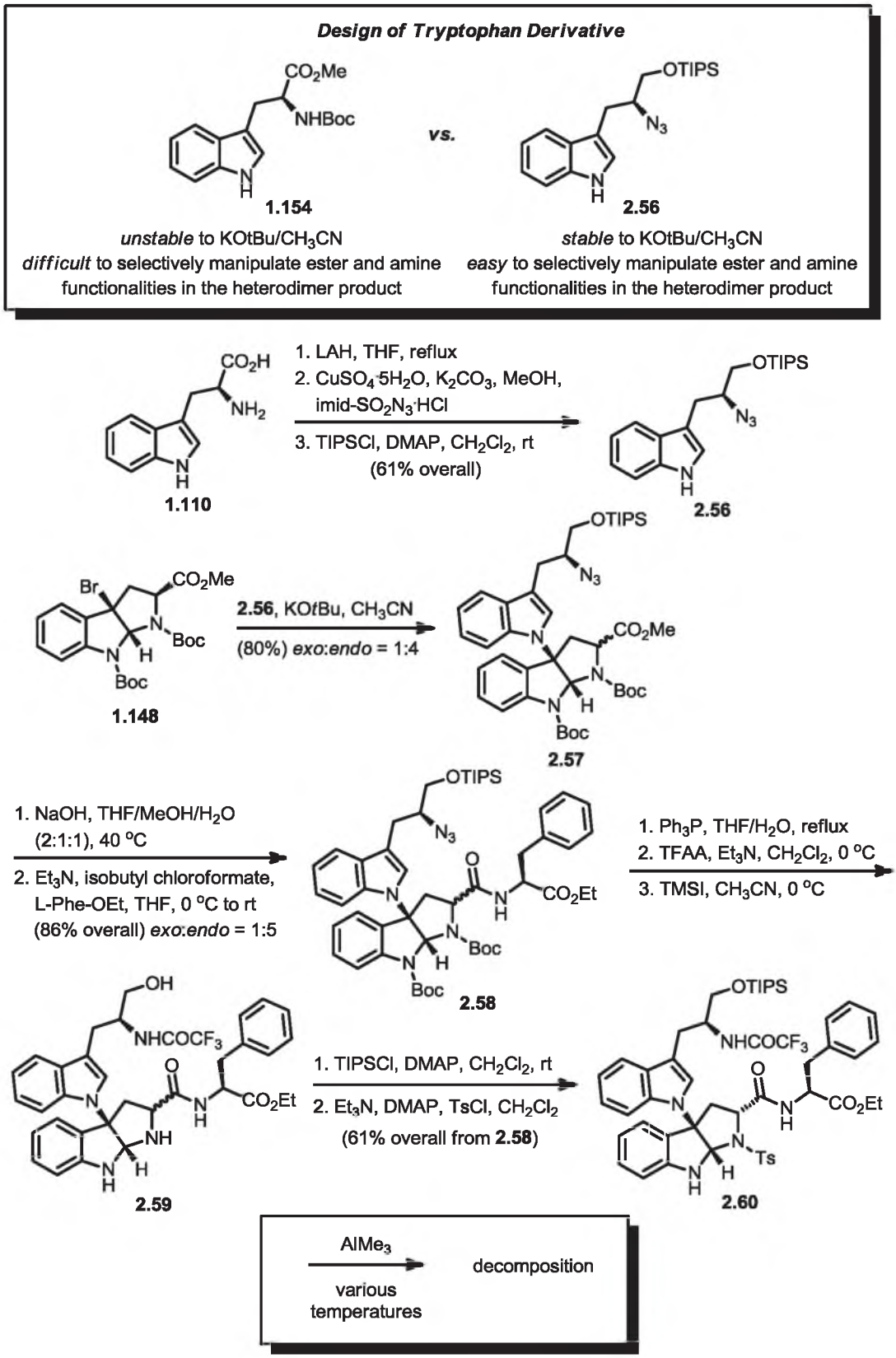


Figure 2.2. Proposed Transition State for Reduction of Enamine **2.43**



Scheme 2.13. Design of Tryptophan **2.56** and Synthesis of **2.60**

manipulation then gave **2.60**.

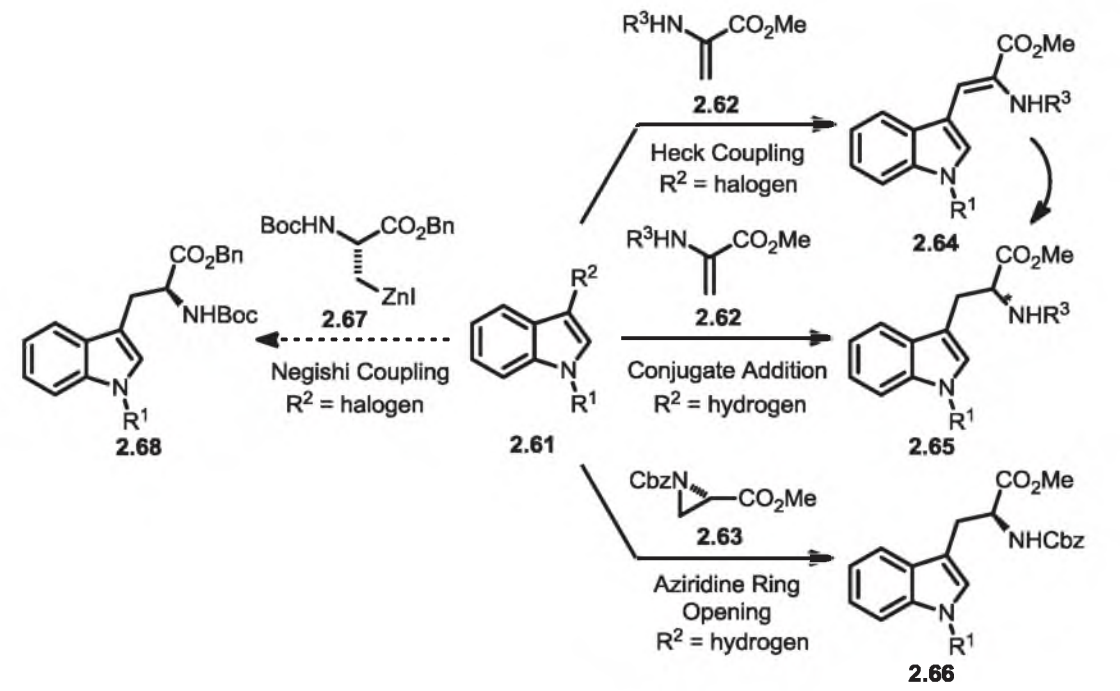
Attempts to affect tandem rearrangement and enamine formation of advanced heterodimer **2.60,** unfortunately, proved fruitless. Given these results, we decided to pursue tetracyclic compound **2.53** for functionalization at the C(3) indolic position in an attempt to perform a tryptophan synthesis from indole.

Tryptophan Synthesis

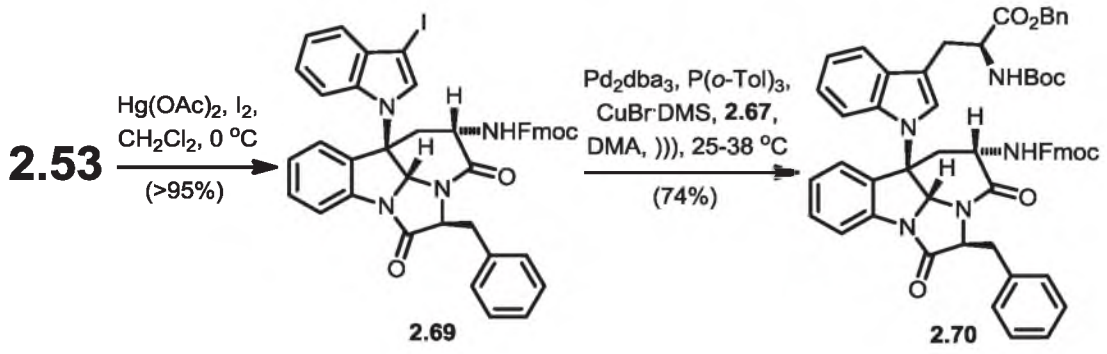
There have been numerous approaches to the synthesis of tryptophan by way of functionalizing the C(3) position of indole (Scheme 2.14).[13] Approaches have included utilizing the high nucleophilicity of the C(3) position to undergo nucleophilic additions to various substrates including unsaturated systems and activated aziridine rings.

The Negishi coupling using serine derived organozinc reagents such as **2.67** and aryl halides to make various phenylalanine derivatives has been reported.[14] We decided to use this methodology toward the synthesis of tryptophan which involved the Negishi coupling of **2.67** with a C(3)-halogen substituted indole (Scheme 2.14). There have been numerous reports in the literature of using these types of organozinc reagents to synthesize various β-substituted-alanine derivatives, but no synthesis of a tryptophan derivative had been reported.[15]

Using the natural C(3) nucleophilicity of indole, **2.53** reacted with mercuric acetate followed by iodine giving iodoindole **2.69** in essentially quantitative conversion (Scheme 2.15). Reaction of **2.69** with organozinc reagent **2.67** under the coupling conditions gave tryptophan **2.70** in 74% yield. The synthesis of compound **2.70** is significant as the coupling of it with different peptides would yield kapakahines E, F, and G.



Scheme 2.14. Various Syntheses of Tryptophans from Indoles



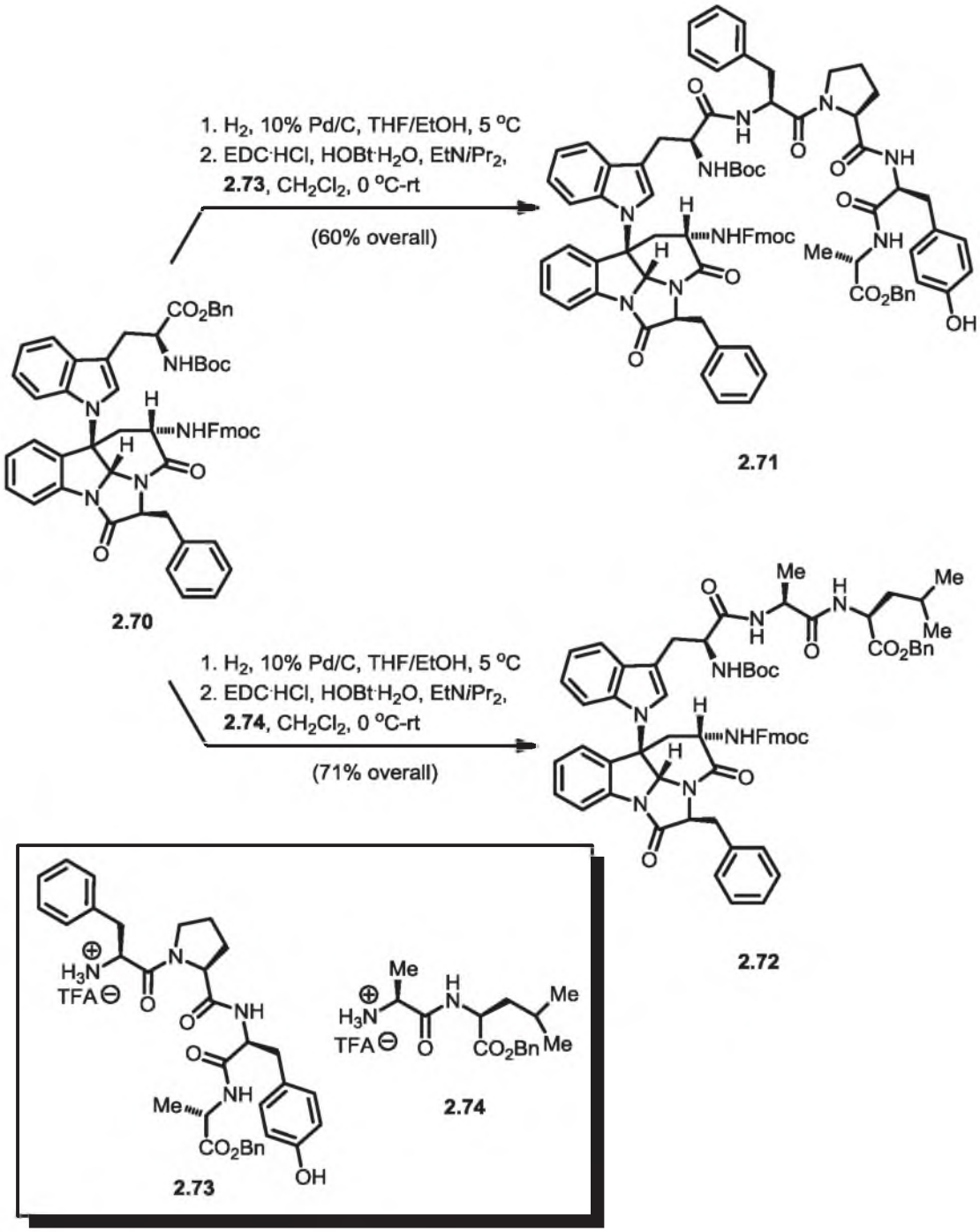
Scheme 2.15. Synthesis of Tryptophan **2.70** using the Negishi Coupling

Endgame

Tryptophan **2.70** was subjected to hydrogenolysis in a mixture of EtOH/THF using 10% Pd/C under hydrogen at atmospheric pressure keeping the mixture at about 5 °C (Scheme 2.16). Such mild conditions were used to prevent the hydrogenolysis of the Fmoc protecting group.[16,17] The Fmoc group was chosen based on its resistance to the hydrogenolysis conditions used for benzyl ester deprotection, and if hydrogenolysis could not be used to induce global deprotection in the final stage, strong amine bases may be used to remove the Fmoc protecting group.[18] The resulting free acid from **2.70** was then coupled to tetrapeptide **2.73** and dipeptide **2.74** to yield macrocyclization precursors **2.71** and **2.72**, respectively (Scheme 2.16).

The next step involved a one-pot global deprotection of both the benzyl ester and Fmoc protecting groups using hydrogenolysis. We wished to avoid strongly nucleophilic amine bases to remove the Fmoc group due to the perceived sensitivity of the strained imidazolone ring toward nucleophiles. A number of additives were employed in the hydrogenolysis step (formic acid, acetic acid, ammonium formate) and it was noted that ammonium formate had a pronounced effect on the efficiency of the hydrogenolysis step. With formic and acetic acid additives, the global deprotection was very sluggish and led to incompletely deprotected material.

The resulting amino acids from **2.71** and **2.72** were subjected to macrolactamization with HATU in CH_2Cl_2/DMF followed by deprotection of the Boc group using TFA in CH_2Cl_2 to afford kapakahine E and kapakahine F, respectively (Scheme 2.17). The total synthesis of kapakahines E and F required 18 steps from L-tryptophan methyl ester hydrochloride (longest linear sequence) and were completed with overall yields of 3.3%



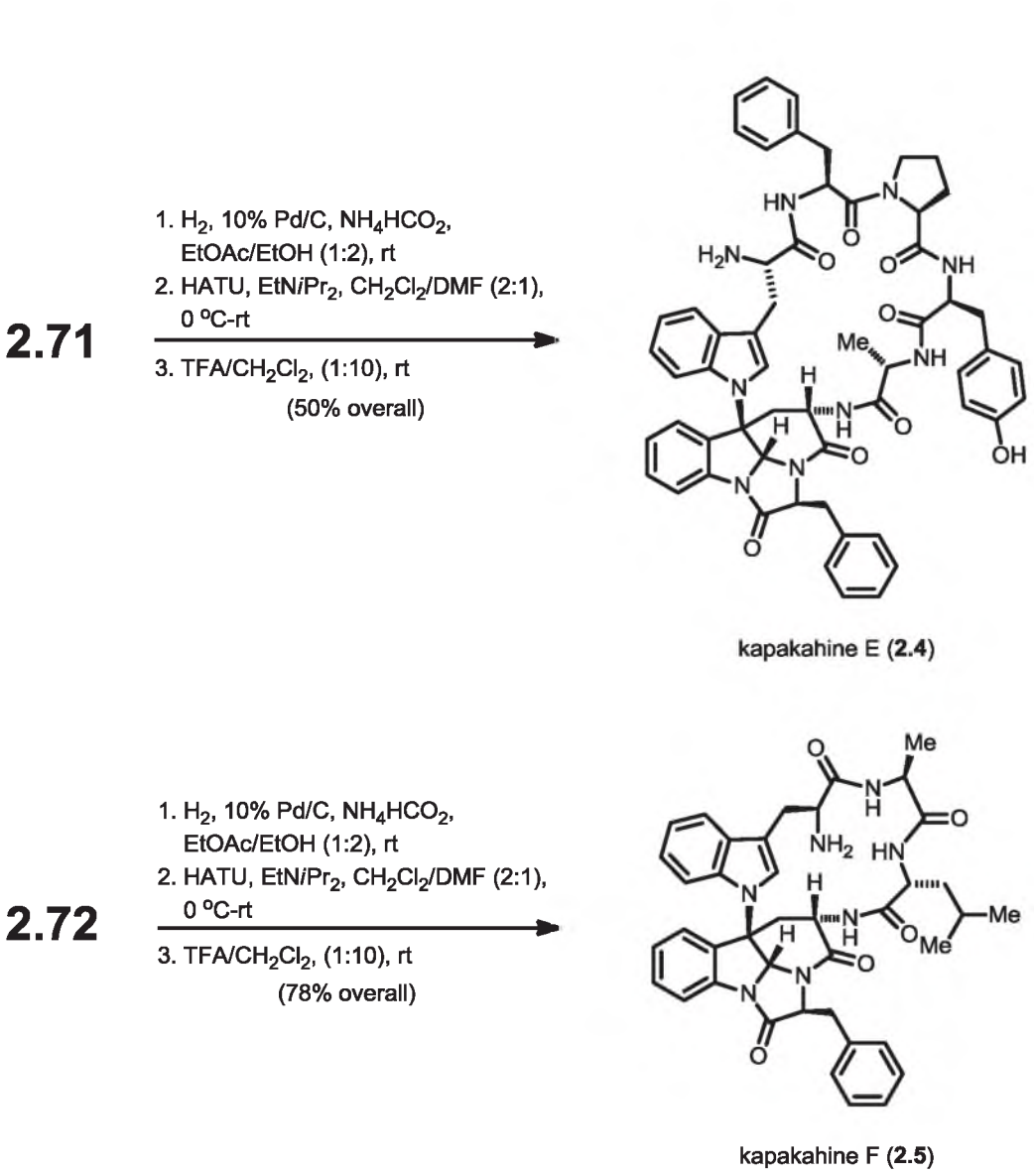
Scheme 2.16. Synthesis of Peptides **2.71** and **2.72**

and 6.0%, respectively.

Kapakahine E represented a problem in terms of matching the NMR spectra of the natural material reported by Nakao, Scheuer, and coworkers due to the non-precise conditions reported for the acquisition of their spectra and the limited quantity of material that they had isolated. After struggling with conditions, we had to rely on HPLC coinjection analysis with the natural material generously provided by Professor Yoichi Nakao, HRMS, and LC-MS/MS as well as matching the spectra of our synthetic kapakahine F to that of synthetic kapakahine F reported by Baran.

Conclusions

A general total synthesis of the kapakahine family has been established and verified by matching the spectra of our synthetic kapakahine E and F to that of natural kapakahine E and synthetic kapakahine F. Verification of the total synthesis of kapakahine E was done using HPLC coinjection analysis and MS/MS fragmentation studies. Verification of the total synthesis of kapakahine F was done by matching the spectra of that reported by the Baran group. In the process, a novel lewis acid mediated rearrangement of pyrroloindolines to α-carbolines with concomitant imidazolone formation has been developed and a synthesis of highly substituted tryptophans from 3-iodo indoles using the Negishi coupling reaction has been established. Biological activities of the synthetic kapakahines are under way.



Scheme 2.17. Total Syntheses of Kapakahines E and F

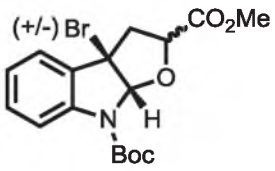
Acknowledgements

We would like to thank the support staff at the University of Utah and especially Dr. James G. Muller for help in acquiring HPLC and MS data, and Dr. Peter Flynn for help in acquiring NMR data. We are grateful to Professor Yoichi Nakao (Waseda University) for generously supplying us with a sample of natural kapakahine E.

Experimental Section

Chemicals were either used as received or purified according to *Purification of Common Laboratory Chemicals*.[19] Glassware was dried in an oven at 130 °C or flame dried and cooled under a dry atmosphere prior to use. All reactions were performed using common dry, inert atmosphere techniques. Reactions were monitored by TLC and visualized by a dual short wave/long wave UV lamp and stained with an ethanolic solution of potassium permanganate or p-anisaldehyde. Column flash chromatography was performed using 230-400 mesh silica gel. NMR spectra were recorded on Varian Unity-300, Varian VXR-500, or Varian Inova-500 spectrometers. Chemical shifts for ^{1}H NMR were reported as δ, parts per million, relative to the signal of tetramethylsilane at 0 ppm. Chemical shifts for ^{13}C NMR were reported as δ, parts per million, relative to the center line signal of the $CDCl_3$ triplet at 77 ppm. Proton and carbon assignments were established using spectral data of similar compounds, ^{1}H nOe analysis, and ^{13}C DEPT NMR. The abbreviations s, bs, d, dd, bd, ddd, t, q, bq, and m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, and multiplet, respectively. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Optical rotations were

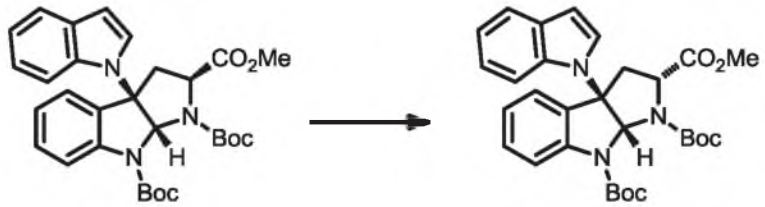
obtained on a Perkin Elmer Model 343 polarimeter (Na D line) using a microcell with a 1 decimeter path length. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 double focusing high resolution mass spectrometer. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg).



2.34

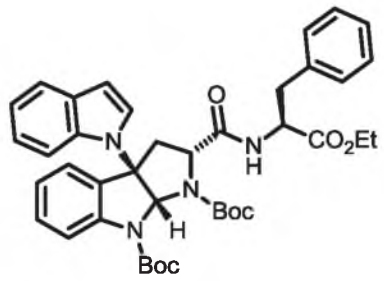
Preparation of (±)-8-*tert*-butyl 2-methyl 3a-bromo-3,3a-dihydro-2*H*-furo[2,3-*b*]indole-2,8(8a*H*)-dicarboxylate (2.34). To a solution of indole lactate **2.33** (0.173 g, 0.541 mmol) in CH_2Cl_2 (10 mL) at rt was added Na_2SO_4 (excess), NBS (0.097, 0.54 mmol), and *p*-TsOH·H_2O (0.010 g, 0.054 mmol). The reaction was quenched after 3 h with 10% aq. $NaHCO_3$ (10 mL) and diluted with CH_2Cl_2 (40 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. Flash chromatography (10% EtOAc:hexanes) afforded 0.051 g (24%) of **2.34**-*exo* and 0.112 g (52%) of **2.34**-*endo* as white foams. **2.34**-*exo*: R_f 0.35 (33% EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (bs, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 8.3 Hz, 1H), 6.38 (bs, 1H), 4.21 (dd, *J* = 10.3, 5.4 Hz, 1H), 3.76 (s, 3H), 3.13 (dd, *J* = 12.7, 4.9 Hz, 1H), 2.99 (dd, *J* = 11.2, 11.2 Hz, 1H), 1.60 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 151.5, 141.3, 131.4, 130.8, 124.7, 124.0, 115.3, 100.9, 82.7, 76.5, 59.8, 52.5, 47.6, 28.3; IR (neat) 2979, 2954, 2932, 1759, 1717, 1604, 1482, 1440, 1388, 1350, 1287, 1253, 1216, 1164, 1068, 1019 cm^{-1}; LRMS (ESI) calcd for $C_{17}H_{20}BrNO_5Na$ *m/z* ($M+Na^+$)

420.1, found 420.0. **2.34**-*endo*: R_f 0.30 (33% EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (bs, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.28 (t, J = 7.3 Hz, 1H), 7.05 (t, J = 7.3 Hz, 1H), 6.26 (bs, 1H), 4.69 (d, J = 8.8 Hz, 1H), 3.34-3.17 (m, 5H), 1.62 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 151.6, 142.6, 130.8, 124.8, 123.7, 115.1, 101.6, 82.5, 78.0, 60.0, 52.4, 47.0, 28.6; IR (neat) 2979, 2952, 2933, 1760, 1721, 1604, 1482, 1446, 1390, 1353, 1166, 1067, 1019 cm^{-1}; LRMS (ESI) calcd for $C_{17}H_{20}BrNO_5Na$ *m/z* ($M+Na^+$) 420.1, found 420.0.



1.149-*exo* **1.149**-*endo*

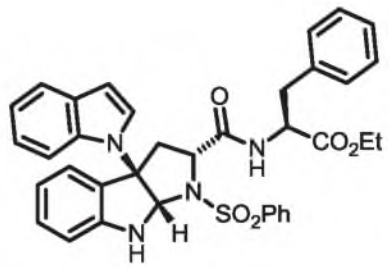
Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-bromo-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.149-*endo*) from (2*S*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-bromo-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (1.149-*exo*). To a solution of **1.149**-*exo* (0.675 g, 1.26 mmol) in THF (7 mL) at −78 °C was added LHMDS (3.8 mL of a 1.0 M solution in THF, 3.8 mmol) dropwise. The reaction mixture was allowed to warm to 0 °C and stirred at 0 °C for 30 min after which it was re-cooled to −78 °C. The reaction was quenched with MeOH, the resulting mixture was concentrated and used directly in the synthesis of **2.41**.



2.41

Preparation of (2*R*,3a*R*,8a*R*)-di-*tert*-butyl 2-(((*S*)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)-3a-(1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,8(2*H*,8a*H*)-dicarboxylate (2.41). To a solution of **1.149**-*endo* (1.609 g, 3.016 mmol) in THF:MeOH:H_2O (2:1:1, 40 mL) was added NaOH (0.483 g, 12.1 mmol). The resulting mixture was heated at 40 °C for 2 h and then cooled to rt. The reaction mixture was diluted with EtOAc (100 mL) and neutralized with citric acid (5% aq., 100 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were washed with H_2O (50 mL) and brine (50 mL). The extracts were dried ($MgSO_4$) and concentrated. To a solution of the resulting residue in THF (12 mL) at 0 °C was added Et_3N (0.84 mL, 6.0 mmol) and isobutyl chloroformate (0.43 mL, 3.3 mmol). After stirring for 5 min, a solution of L-phenylalanine ethyl ester (1.166 g, 6.032 mmol) in EtOAc (10 mL) was added at once. The resulting mixture was allowed to warm to rt and then diluted with CH_2Cl_2 (150 mL). The reaction was quenched with citric acid (5% aq., 50 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The organic extracts were washed with H_2O (50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (25% EtOAc:hexanes) afforded 1.781 g (85% overall) of **2.41** as a white foam. **2.41**: R_f 0.5 (33% EtOAc:hexanes); $[\alpha]_D$ = +78.9° (*c* = 0.096, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.60 (m, 1H), 7.46 (d, *J* = 8.1 Hz,

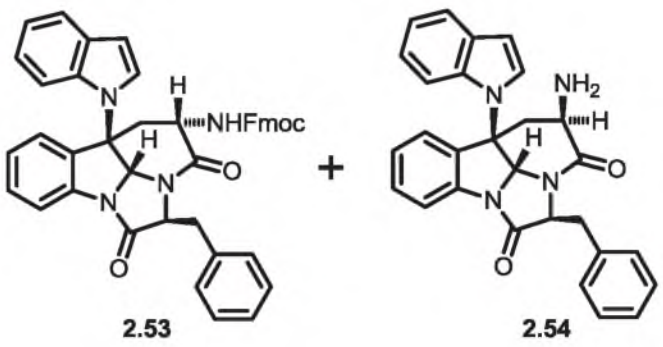
1H), 7.36 (dd, J = 7.8, 0.9 Hz, 1H), 7.26-7.04 (m, 10H), 7.01 (d, J = 7.4 Hz, 1H), 6.90 (d, J = 6.7 Hz, 1H), 6.86 (s, 1H,), 6.42 (dd, J = 3.6, 0.3 Hz, 1H), 4.93 (dd, J = 9.0, 1.5 Hz, 1H), 4.21-3.99 (m, 3H), 3.42 (dd, J = 13.0, 8.8 Hz, 1H), 3.27 (dd, J = 13.0, 1.4 Hz, 1H), 2.99 (dd, J = 13.6, 5.7 Hz, 1H), 2.92 (dd, J = 13.6, 5.3 Hz, 1H), 1.52 (s, 9H), 1.50 (s, 9H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 169.4, 154.0, 151.7, 142.4, 135.8, 134.4, 130.5, 130.4, 129.4, 129.1, 128.2, 126.8, 126.2, 126.0, 123.7, 122.0, 121.6, 120.1, 117.1, 111.4, 101.9, 82.3, 82.3, 81.0, 73.1, 62.0, 61.2, 53.5, 38.5, 38.1, 28.1, 14.1; IR (neat) 3408, 2979, 1718, 1513, 1482, 1456, 1371, 1328, 1255, 1157, 1016 cm^{-1}; LRMS (ESI) calcd for $C_{40}H_{47}N_4O_7$ *m/z* ($M+H^+$) 695.3, found 695.4.



2.42

Preparation of (*S*)-ethyl 2-((2*R*,3a*R*,8a*S*)-3a-(1*H*-indol-1-yl)-1-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxamido)-3-phenylpropanoate (2.42). To a solution of amide **2.41** (1.781 g, 2.563 mmol) in CH_3CN (12 mL) at 0 °C was added TMSI (1.76 mL, 12.8 mmol) dropwise. The reaction was quenched after 1 h with sat. $NaHCO_3$ (aq, 50 mL) and diluted with CH_2Cl_2 (150 mL) and brine (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ (aq, 50 mL) and brine (50 mL). The extracts were dried ($MgSO_4$) and concentrated. To a solution of the resulting residue that contained the crude

bis-amine from **2.41** in CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (0.71 mL, 5.1 mmol), DMAP (0.157 g, 1.28 mmol), and $PhSO_2Cl$ (0.49 mL, 3.8 mmol). The reaction mixture was stirred at 0 °C until complete consumption of the starting material was observed by TLC upon which the mixture was diluted with CH_2Cl_2 (100 mL). The reaction was quenched with 5% citric acid (aq, 20 mL) and the aqueous phase was washed with CH_2Cl_2 (50 mL). The organic phases were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (25% EtOAc:hexanes) afforded 1.381 g (85% overall) of **2.42** as a white foam. **2.42**: R_f 0.40 (33% EtOAc:hexanes); $[\alpha]_D$ = +84.4° (*c* = 0.428, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.4, 1.0 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2 H), 7.53 (d, *J* = 7.9 Hz, 1 H), 7.33-7.26 (m, 3H), 7.20-7.08 (m, 5H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.81-6.75 (m, 2H), 6.69 (d, *J* = 3.3 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.28 (d, *J* = 8.4 Hz, 1H), 6.24 (d, *J* = 3.6 Hz, 1H), 5.84 (s, 1H), 4.97 (s, 1H), 4.56 (dd, *J* = 9.0, 2.6 Hz, 1H), 4.24 (dd, *J* = 13.3, 6.0 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.24 (dd, *J* = 13.8, 9.3 Hz, 1H), 3.07 (dd, *J* = 13.6, 2.6 Hz, 1H), 3.01 (d, *J* = 5.9 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 169.3, 148.2, 136.8, 135.7, 134.0, 133.9, 130.6, 130.6, 129.9, 129.6, 128.4, 127.4, 126.9, 126.2, 125.7, 125.6, 121.6, 121.6, 120.0, 119.8, 111.4, 111.0, 101.8, 83.0, 74.4, 62.8, 61.2, 53.5, 38.2, 38.1, 14.0; IR (neat) 3403, 3060, 2981, 1737, 1670, 1611, 1516, 1472, 1452, 1352, 1208, 1168, 1119, 1092, 1069, 1027, 910 cm^{-1}; LRMS (ESI) calcd for $C_{36}H_{35}N_4O_5S$ *m/z* ($M+H^+$) 635.2. found 635.3.

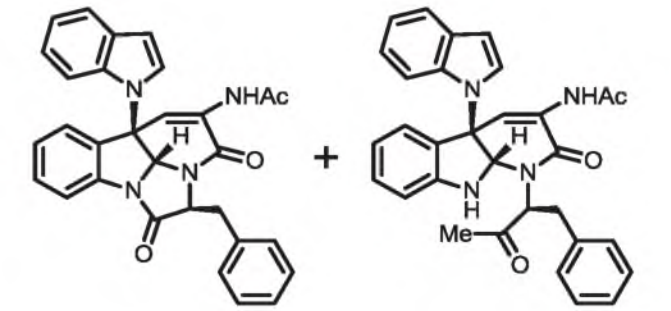


Preparation of (9*H*-fluoren-9-yl)methyl ((2*S*,2a^1*R*,4*S*,5a*R*)-2-benzyl-5a-(1*H*-indol-1-yl)-1,3-dioxo-2,2a^1,3,4,5,5a-hexahydro-1*H*-2a,9b-diazacyclopenta[*jk*]fluoren-4-yl)carbamate (2.53) and (2*S*,2a^1*R*,4*R*,5a*R*)-4-amino-2-benzyl-5a-(1*H*-indol-1-yl)-2a^1,4,5,5a-tetrahydro-1*H*-2a,9b-diazacyclopenta[*jk*]fluorene-1,3(2*H*)-dione (2.54). To a solution of **2.42** (0.399 g, 0.628 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added $AlMe_3$ (1.1 mL of a 2.0 M solution in PhMe, 2.2 mmol) dropwise. The resulting mixture was stirred for 0.5 h, allowed to warm to rt for 1 h and then sonicated to 32 °C in an ultrasonic cleaning bath. The mixture was then cooled to 0 °C and another aliquot of $AlMe_3$ (1.1 mL of a 2.0 M solution in PhMe, 2.2 mmol) was added dropwise. The mixture was stirred for an additional 0.5 h, allowed to warm to rt for 1 h and then sonicated to maintain a temperature between 26-32 °C. After consumption of the starting material (TLC) the mixture was cooled to 0 °C and the reaction was quenched using Rochelle's salt (30% aq, 2 mL). The resulting mixture was allowed to stir for 0.5 h after which it was diluted with CH_2Cl_2 (150 mL). The mixture was washed with brine (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed again with brine (50 mL), dried ($MgSO_4$) and concentrated to afford an inseparable mixture of **2.43** and **2.44** (1.5:1.0) as a pale yellow oil.

To a solution of **2.43** and **2.44** from above in CH_2Cl_2 (12 mL) at 0 °C was added

AcOH (0.8 mL, 1.25 mL/mmol starting amide) followed by $NaCNBH_3$ (0.190 g, 2.83 mmol). The resulting mixture was allowed to stir until the starting material was consumed (TLC). The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and washed with sat. $NaHCO_3$ (aq, 50 mL) and brine (50 mL). After gas evolution had ceased, FmocCl (0.244 g, 0.942 mmol) was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organics were washed with sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (15-50% EtOAc:hexanes) afforded 0.145 g (33% overall) of **2.53** as a colorless glass and 0.042 g (16% overall) of **2.54** also as a colorless glass. **2.53**: R_f 0.20 (33% EtOAc:hexanes); $[\alpha]_D$ = −69.3 (*c* = 0.494, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 3.4 Hz, 1H), 7.72-7.69 (m, 3H), 7.60-7.55 (m, 3H), 7.37-7.23 (m, 6H), 7.18 (d, *J* = 7.0 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 2H), 7.01 (t, *J* = 7.5 Hz, 2H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 3.0 Hz, 1H), 6.24 (d, *J* = 8.4 Hz, 1H), 6.20 (d, *J* = 4.0 Hz, 1H), 5.56 (s, 1H), 5.14 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.47-4.40 (m, 2H), 4.22 (dd, *J* = 7.2 Hz, 1H), 3.62 (dd, *J* = 14.8, 2.9 Hz, 1H), 3.24 (dd, *J* = 14.3, 5.8 Hz, 1H), 3.19 (dd, *J* = 14.3, 5.5 Hz, 1H), 1.90 (dd, *J* = 14.6, 13.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 167.0, 156.1, 143.5, 143.4, 141.2, 141.2, 137.7, 134.8, 134.4, 134.1, 130.3, 130.3, 129.1, 128.5, 127.7, 127.5, 127.4, 127.0, 127.0, 126.4, 126.2, 125.0, 124.9, 124.6, 123.7, 121.8, 121.2, 120.1, 120.0, 119.9, 114.8, 110.8, 103.2, 81.7, 67.2, 65.1, 65.1, 48.5, 46.9, 37.3, 36.3; IR (neat) 3400, 3063, 1726, 1679, 1484, 1456, 1342, 1295, 1219, 1078 cm^{-1}; LRMS (ESI) calcd for $C_{43}H_{34}N_4O_4Na$ *m/z* ($M+Na^+$) 693.3, found 693.2. **2.54**: R_f 0.25 (50% EtOAc:hexanes); $[\alpha]_D$ = −216.6 (*c* = 0.216, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.85 (d, *J* = 3.6 Hz, 1H), 7.62 (d, *J* = 8.0

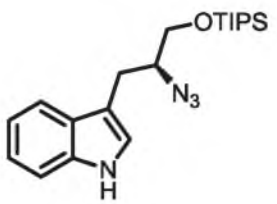
Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.36-7.30 (m, 1H), 7.22 (d, J = 7.5 Hz, 2H), 7.08 (t, J = 7.5 Hz, 2H), 6.99-6.94 (m, 3H), 6.84-6.80 (m, 1H), 6.75 (t, J = 7.5 Hz, 1H), 6.62 (d, J = 3.5 Hz, 1H), 6.14 (d, J = 8.3 Hz, 1H), 5.43 (s, 1H), 5.10 (dd, J = 5.0, 5.0 Hz, 1H), 3.78 (dd, J = 13.2, 2.6 Hz, 1H), 3.70 (dd, J = 14.9, 2.5 Hz, 1H), 3.17 (dd, J = 14.0, 5.5 Hz, 1H), 2.29 (dd, J = 14.5, 14.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.7, 168.5, 139.9, 136.8, 136.1, 135.8, 132.0, 131.7, 130.7, 129.8, 128.9, 127.5, 126.4, 125.1, 123.1, 122.5, 121.4, 115.9, 112.2, 104.2, 83.4, 66.9, 66.9, 53.1, 37.5, 34.8; IR (neat) 3189, 2421, 1732, 1680, 1603, 1484, 1458, 1294, 1217, 1136 cm^{-1}; LRMS (ESI) calcd for $C_{28}H_{24}N_4O_2$ *m/z* ($M+H^+$) 449.2, found 449.2.



2.43-acetamide **2.44-acetamide**

Characterization of 2.43 and 2.44 as their Acetamide: Preparation of *N*-((2*S*,2a^1*R*,5a*R*)-2-benzyl-5a-(1*H*-indol-1-yl)-1,3-dioxo-2,2a^1,3,5a-tetrahydro-1*H*-2a,9b-diazacyclopenta[*jk*]fluoren-4-yl)acetamide (2.43-acetamide) and *N*-((4a*R*,9a*S*)-4a-(1*H*-indol-1-yl)-2-oxo-1-((*S*)-3-oxo-1-phenylbutan-2-yl)-2,4a,9,9a-tetrahydro-1*H*-pyrido[2,3-*b*]indol-3-yl)acetamide (2.44-acetamide). To a mixture of **2.43** and **2.44** (0.044 g) in CH_2Cl_2 (2 mL) at 0 °C was added Et_3N (30 μL) and AcCl (14 μL). After 0.5 h the mixture was diluted with CH_2Cl_2 (40 mL) and the reaction was quenched with citric acid (5% aq, 10 mL). The organic phase was washed with brine, dried ($MgSO_4$), and

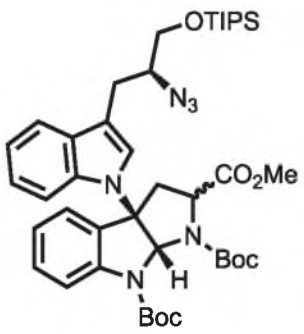
concentrated. Flash chromatography (15-25% EtOAc:hexanes) afforded 0.030 g (61%) of **2.43**-acetamide as an oil and 0.010 g (20%) of **2.44**-acetamide as an oil. **2.43**-acetamide: R_f 0.29 (33% EtOAc:hexanes); $[\alpha]_D = -23.1°$ (*c* = 0.200, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.78 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.47 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.25-7.22 (m, 3H), 7.18-7.14 (m, 4H), 7.10-7.06 (m, 2H), 6.86 (bs, 1H), 6.48 (d, *J* = 3.5 Hz, 1H), 5.55 (s, 1H), 5.08 (dd, *J* = 8.4, 5.0 Hz, 1H), 3.27 (dd, *J* = 14.5, 5.2 Hz, 1H), 3.17 (dd, *J* = 14.1, 8.5 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 169.2, 159.2, 139.1, 135.3, 134.3, 132.4, 131.3, 130.9, 129.0, 128.6, 127.3, 126.3, 126.0, 126.0, 125.8, 122.2, 121.6, 120.5, 116.4, 115.3, 111.2, 102.6, 80.7, 66.7, 63.4, 34.5, 24.6; IR (neat) 3371, 3064, 1737, 1668, 1511, 1481, 1450, 1367, 1293, 1232, 1195, 1017 cm^{-1}; LRMS (ESI) calcd for $C_{30}H_{24}N_4O_3Na$ *m/z* ($M+Na^+$) 511.2, found 511.2. **2.44**-acetamide: R_f 0.19 (33% EtOAc:hexanes); $[\alpha]_D = -154.2$ (*c* = 0.076, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.37 (s, 1H), 7.23-7.16 (m, 5H), 7.06 (t, *J* = 7.0 Hz, 1H), 6.95-6.91 (m, 2H), 6.88-6.87 (m, 2H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 3.4 Hz, 1H), 5.58 (d, *J* = 4.5 Hz, 1H), 4.73 (broad s, 1H), 4.23 (bs, 1H), 3.06 (dd, *J* = 14.3, 6.0 Hz, 1H), 2.63 (dd, *J* = 14.4, 9.3 Hz, 1H), 2.14 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 173.0, 169.0, 161.0, 146.6, 136.4, 134.0, 130.8, 129.7, 129.0, 128.8, 127.2, 127.0, 126.6, 124.7, 121.5, 121.4, 121.2, 120.0, 113.9, 112.6, 110.3, 102.3, 77.4, 66.6, 65.3, 33.8, 28.8, 24.7; IR (neat) 3371, 2925, 1719, 1640, 1514, 1453, 1308, 1224, 1030 cm^{-1}; LRMS (ESI) calcd for $C_{31}H_{28}N_4O_3Na$ *m/z* ($M+Na^+$) 572.2, found 527.2.



2.56

Preparation of (*S*)-3-(2-azido-3-((triisopropylsilyl)oxy)propyl)-1*H*-indole (2.56). To a suspension of L-tryptophan (1.000 g, 4.90 mmol) in THF (25mL) at 0 °C was cautiously added lithium aluminum hydride (0.743 g, 0.020 mmol) and allowed to warm to rt and refluxed overnight. After cooling to 0 °C, the mixture was quenched by the addition of sat. Na_2SO_4 and partitioned between EtOAc (100 mL) and H_2O (50 mL). The aqueous layer was separated and extracted with EtOAc (5 x 25 mL) and the organic extracts were combined and washed with H_2O (15 mL), brine (25 mL), dried (Na_2SO_4), and concentrated to afford 0.793 g of crude amino alcohol. To the crude material in MeOH (25 mL) was added K_2CO_3 (1.165 g, 8.43 mmol), $CuSO_4 \cdot 5H_2O$ (0.011 g, 0.0421 mmol), and imid-$SO_2N_3 \cdot HCl$ (1.05 g, 5.06 mmol). The mixture was stirred for 6 h, concentrated, diluted with CH_2Cl_2 (50 mL) and washed with dilute HCl (10 mL), H_2O (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated to afford 0.681 g of crude azido alcohol. To the crude material in CH_2Cl_2 (12 mL) was added DMAP (1.54 g, 12.6 mmol) and ~90% TIPSCl (1.2 mL). After stirring at rt overnight, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with dilute HCl (10 mL), H_2O (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (5% EtOAc:hexanes) afforded 1.11 g (61% overall) of **2.56**. **2.56**: oil; R_f 0.53 (20% EtOAc:hexanes); $[\alpha]_D = -14.1$ (c = 2.714, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (bs, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.21 (dt, J = 6.9, 1.2 Hz, 1H), 7.16-7.08 (m, 2H), 3.87 (dd, J =

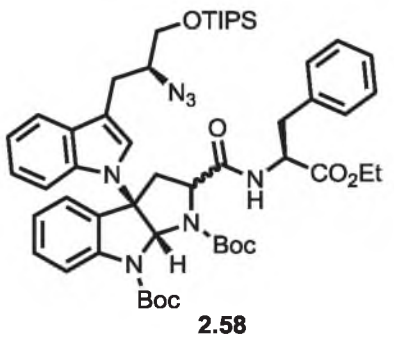
10.2, 4.2 Hz, 1H), 3.79 (dd, J = 10.2, 5.7 Hz, 1H), 3.74-3.64 (m, 1H), 3.08 (dd, J = 14.7, 6.0 Hz, 1H), 2.93 (dd, J = 15.0, 7.8 Hz, 1H), 1.16-1.03 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 127.3, 122.7, 122.0, 119.4, 118.6, 111.7, 111.2, 66.1, 63.8, 26.2, 17.9, 17.6, 11.8; IR (neat) 3418, 2942, 2866, 2360, 2342, 2105, 1457, 1253, 1120, 882 cm^{-1}; LRMS (ESI) calcd for $C_{20}H_{32}N_4OSiNa$ *m/z* ($M+Na^+$) 395.2, found 395.2.



2.57

Preparation of (3a*R*,8a*R*)-1,8-di-tert-butyl 2-methyl 3a-(3-((*S*)-2-azido-3-((triisopropylsilyl)oxy)propyl)-1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (2.57). To a solution of **1.148** (0.444 g, 0.892 mmol) and **2.56** (0.220 g, 0.600 mmol) in CH_3CN (6 mL) at 0 °C was added dropwise KO*t*Bu (1.2 mL, 1M solution in THF, 1.2 mmol). The mixture was stirred for 15 min. and then quenched with sat. $NaHCO_3$ (1 mL), concentrated, and diluted with CH_2Cl_2 (50 mL). The solution was washed with brine (15 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (10% EtOAc:hexanes) afforded 0.378 g (80%) of **2.57** as a mixture (4:1) of *endo* and *exo* isomers, respectively. **2.57**-*endo* isomer: foam; R_f 0.40 (20% EtOAc:hexanes); $[\alpha]_D$ = +22.0 (c = 1.246, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (bs, 1H), 7.59 (d, 7.5 Hz, 1H), 7.37 (t, J = 7.0 Hz, 1H), 7.30 (d, J = 7.0 Hz, 1H), 7.25 (d, J = 6.0 Hz, 1H), 7.19 (t, J = 6.5 Hz, 1H, 7.14 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H),

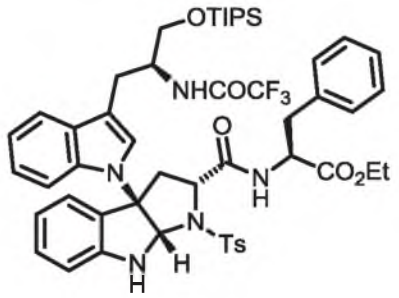
6.85 (s, 1H), 6.78 (s, 1H), 4.91 (bs, 1H), 3.79 (dd, J = 10.0, 4.0 Hz, 1H), 3.73 (dd, J = 10.5, 6.0 Hz, 1H), 3.64-3.58 (m, 1H), 3.52 (dd, J = 13.0, 9.0 Hz, 1H), 3.23 (s, 3H), 3.03 (d, J = 13.0 Hz, 1H), 2.95 (dd, J = 15.0, 6.0 Hz, 1H), 2.80 (dd, J = 15.0, 8.0 Hz, 1H), 1.53 (s, 9H), 1.50 (s, 9H), 1.1-1.0 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 151.9, 151.9, 143.6, 134.9, 130.9, 130.0, 129.2, 125.3, 124.8, 123.4, 122.3, 119.9, 119.4, 117.7, 111.6, 111.2, 82.0, 82.0, 79.9, 72.6, 66.0, 63.8, 59.4, 52.1, 38.9, 28.3, 28.2, 26.2, 17.9, 11.9; IR (neat) 2943, 2866, 2100, 1718, 1481, 1457, 1393, 1368, 1257, 1159, 1016, 752; LRMS (ESI) calcd for $C_{42}H_{60}N_6O_7SiNa$ *m/z* ($M+Na^+$) 811.4, found 811.4.



2.58

Preparation of (3a*R*,8a*R*)-di-*tert*-butyl 3a-(3-((*S*)-2-azido-3-((triisopropylsilyl)oxy)propyl)-1*H*-indol-1-yl)-2-(((*S*)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,8(2*H*,8a*H*)-dicarboxylate (2.58). To a solution of **2.57** (0.493 g, 0.627 mmol) in THF/MeOH/H_2O (20 mL, 1:1:1) at rt was added NaOH (0.156 g, 3.90 mmol). The mixture was stirred for 2 h at 40 °C, then cooled to rt and diluted with EtOAc (60 mL). The organic layer was washed with 5% citric acid (20 mL) and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with H_2O (10 mL), brine (25 mL), dried ($MgSO_4$), and concentrated to afford 0.484 g (100%) of acid. The acid was

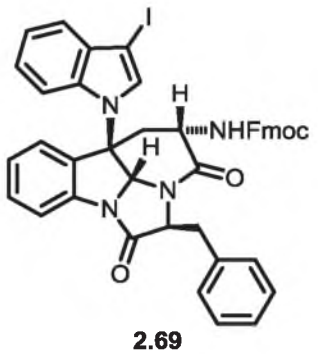
dissolved in THF (6 mL) and Et_3N (0.18 mL, 1.25 mmol) was added dropwise at 0°C followed by isobutyl chloroformate (0.090 mL, 0.69 mmol). After stirring for 5 min, a solution of L-phenylalanine ethyl ester (0.363 g, 1.88 mmol) in EtOAc (6 mL) was added at once. The resulting mixture was allowed to warm to rt and then diluted with CH_2Cl_2 (100 mL). The reaction was quenched with citric acid (5% aq., 50 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The organic extracts were washed with H_2O (25 mL), and brine (25 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (20% EtOAc:hexanes) afforded 0.504 g (86% overall) of **2.58** as a mixture (5:1) of *endo* and *exo* isomers. **2.58**-*endo*: foam; R_f 0.36 (20% EtOAc:hexanes); $[\alpha]_D$ = +34.1 (*c* = 1.974, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H, 7.28-7.12 (m, 7H), 7.10-7.02 (m, 3H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 6.84 (s, 1H), 4.93 (d, *J* = 8.4 Hz, 1H), 4.20-4.05 (m, 2H), 4.01 (dd, *J* = 12.0, 5.7 Hz, 1H), 3.79 (dd, *J* = 10.2, 4.5 Hz, 1H), 3.72 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.61 (p, *J* = 5.4 Hz, 1H), 3.40 (dd, *J* = 12.9, 9.0 Hz, 1H), 3.25 (d, *J* = 12.6 Hz, 1H), 3.02-2.88 (m, 3H), 2.80 (dd, *J* = 14.7, 7.2 Hz, 1H), 1.52 (s, 9H), 1.50 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.11-1.01 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.4, 154.0, 151.7, 142.4, 135.8, 134.8, 130.4, 129.9, 129.4, 129.0, 128.2, 126.8, 126.0, 124.8, 123.7, 122.2, 119.8, 119.5, 117.1, 111.5, 111.1, 82.3, 82.2, 81.0, 73.0, 65.9, 63.6, 62.0, 61.2, 53.6, 38.5, 38.1, 28.1, 28.1, 17.9, 14.1, 11.8; IR (neat) 3408, 3336, 2942, 2867, 2099, 1721, 1510, 1457, 1369, 1255, 1157, 882, 740 cm^{-1}; LRMS (ESI) calcd for $C_{52}H_{71}N_7O_8SiNa$ *m/z* ($M+Na^+$) 972.5, found 972.5.



2.60

Preparation of (*S*)-ethyl 3-phenyl-2-((2*R*,3a*R*,8a*S*)-1-tosyl-3a-(3-((*S*)-2-(2,2,2-trifluoroacetamido)-3-((triisopropylsilyl)oxy)propyl)-1*H*-indol-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxamido)propanoate (2.60). To a solution of **2.58** (0.500 g, 0.536 mmol) in THF/ H_2O (11 mL, 10:1) at rt was added PPh_3 (0.169 g, 0.643 mmol) and the mixture refluxed for 3 h. The mixture was concentrated, diluted with CH_2Cl_2 (50 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated to afford crude amine. The crude amine was dissolved in CH_2Cl_2 (10 mL) and Et_3N (0.11 mL, 0.80 mmol) was added dropwise at 0 °C followed by TFAA (0.076 mL, 0.54 mmol). After stirring for 5 min, the mixture was diluted with CH_2Cl_2 (40 mL). The organic layer was washed with 5% citric acid (10 mL), H_2O (5 mL), brine (10 mL), dried ($MgSO_4$), and concentrated to afford crude trifluoroacetamide. To the crude trifluoroacetamide in CH_3CN (4 mL) at 0 °C was added TMSI (0.29 mL, 0.50 mmol). The mixture was stirred at 0 °C for 0.5 h and then quenched with sat. $NaHCO_3$ (1 mL), concentrated, and diluted with CH_2Cl_2 (50 mL). The organic solution was washed with brine (10 mL), dried ($NaSO_4$), and concentrated to afford crude bisamine **2.59**. To the crude material in DCM (12 mL) was added DMAP (0.131 g, 1.07 mmol) and ~90% TIPSCl (0.3 mL). After stirring at rt overnight, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with dilute HCl (10 mL), H_2O (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated. The

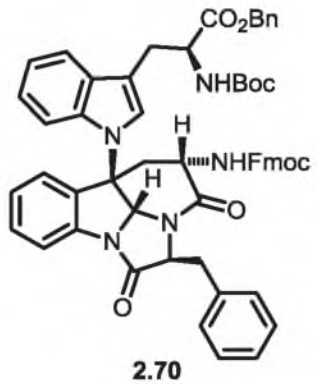
residue was dissolved in CH_2Cl_2 (5 mL) and Et_3N (0.15 mL, 1.1 mmol), DMAP (0.013 g, 0.11 mmol), and TsCl (0.153 g, 0.804 mmol) were added at rt. The mixture was stirred until completion (TLC) and then diluted with CH_2Cl_2 (40 mL). The organic layer was washed with 5% citric acid (10 mL), H_2O (5 mL), brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (20% EtOAc:hexanes) afforded 0.318 g (61% overall) of **2.60** as the *endo* isomer. **2.60**: foam; R_f 0.50 (33% EtOAc:hexanes); $[\alpha]_D$ = +17.4 (*c* = 0.718, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.30-7.26 (m, 2H), 7.25-7.20 (m, 1H), 7.17-7.05 (m, 6H), 6.81 (t, *J* = 7.5 Hz, 1H), 6.74 (t, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.50 (s, 1H), 6.21 (d, *J* = 8.0 Hz, 1H), 5.72 (s, 1H), 4.98 (s, 1H), 4.55 (dd, *J* = 9.5, 2.0 Hz, 1H), 4.19-4.14 (m, 2H), 4.07 (q, *J* = 7.5 Hz, 2H), 3.65 (dd, *J* = 10.0, 2.5 Hz, 1H), 3.57 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.23 (dd, *J* = 13.5, 9.5 Hz, 1H), 3.10 (d, *J* = 13.5 Hz, 1H), 3.02-2.92 (m, 2H), 2.91-2.80 (m, 2H), 2.58 (s, 3H), 1.17 (t, *J* = 7.5 Hz, 3H), 1.10-0.90 (m, 21H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 169.3, 148.5, 145.1, 135.7, 134.3, 133.9, 130.8, 130.6, 130.1, 129.6, 128.3, 127.7, 126.9, 125.9, 125.2, 125.1, 121.7, 120.1, 119.9, 119.8, 111.7, 111.0, 110.1, 82.3, 74.1, 62.6, 62.0, 61.2, 53.6, 51.1, 38.4, 37.3, 26.1, 21.8, 17.9, 14.0, 11.8; IR (neat) 3404, 3310, 2944, 2867, 1724, 1668, 1613, 1522, 1470, 1351, 1208, 1166, 1121, 1030, 883, 739 cm^{-1}; LRMS (ESI) calcd for $C_{51}H_{62}N_5O_7SSiNa$ *m/z* ($M+Na^+$) 996.4, found 996.4.



2.69

Preparation of (9*H*-fluoren-9-yl)methyl ((2S,2a^1*R*,4*S*,5a*R*)-2-benzyl-5a-(3-iodo-1*H*-indol-1-yl)-1,3-dioxo-2,2a^1,3,4,5,5a-hexahydro-1*H*-2a,9b-diazacyclopenta[*jk*]fluoren-4-yl)carbamate (2.69). To a solution of **2.53** (0.100 g, 0.149 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added $Hg(OAc)_2$ (0.071 g, 0.22 mmol). The resulting mixture was allowed to warm to rt for 0.5 h. Once the starting material had been consumed (TLC), the mixture was cooled to 0 °C and 1.1 eq I_2 (0.045 g, 0.16 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The reaction mixture was immediately diluted with CH_2Cl_2 (100 mL) and the reaction was quenched with sat. sodium bisulfite (aq, 15 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (15% EtOAc:hexanes) afforded 0.119 g (100%) of **2.69** as a colorless glass. **2.69**: R_f 0.33 (33% EtOAc:hexanes); $[\alpha]_D = -102.6°$ (*c* = 0.900, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 1H), 7.61 (d, *J* = 7.1 Hz, 1H), 7.41-7.29 (m, 6H), 7.21 (d, *J* = 7.3 Hz, 2H), 7.12-7.08 (m, 3H), 7.02-6.95 (m, 2H), 6.86 (t, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.17 (d, *J* = 8.4 Hz, 1H), 6.15 (d, *J* = 3.7 Hz, 1H), 5.39 (s, 1H), 5.16 (dd, *J* = 5.0, 5.0 Hz, 1H), 4.51 (dd, *J* = 11.6, 7.1 Hz, 1H), 4.48 (dd, *J* = 9.8, 7.5 Hz, 1H), 4.41 (dt, *J* = 12.7, 3.0 Hz, 1H), 4.25 (dd, *J* = 7.5, 7.5 Hz, 1H), 3.63 (dd, *J* = 14.9, 2.7 Hz, 1H), 3.28 (dd, *J* = 14.2, 5.3 Hz, 1H), 3.21 (dd, *J* = 14.2, 5.2 Hz, 1H),1.95 (dd, *J* = 14.8, 12.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$)

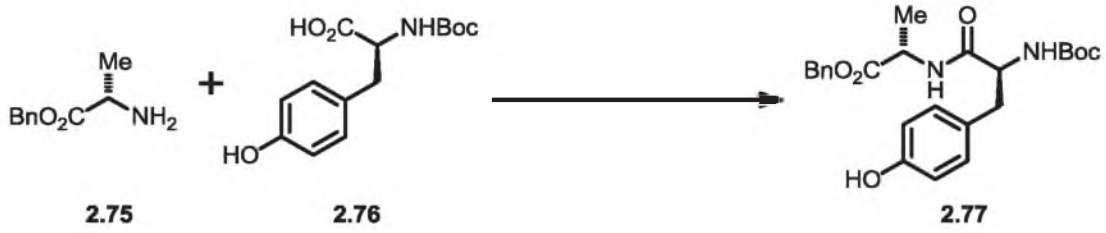
δ 170.4, 167.0, 156.1, 143.6, 143.5, 141.3, 141.3, 137.7, 134.8, 134.1, 133.9, 132.1, 130.7, 130.6, 129.2, 128.6, 127.8, 127.7, 127.7, 127.1, 127.0, 126.4, 125.1, 125.0, 123.8, 123.0, 121.8, 121.1, 120.0, 120.0, 115.0, 110.9, 81.8, 67.4, 65.8, 65.2, 58.8, 48.5, 47.0, 37.3, 36.4; IR (neat) 3395, 3117, 2925, 2854, 1732, 1680, 1484, 1453, 1334, 1297, 1220, 1083, cm^{-1}; LRMS (ESI) calcd for $C_{43}H_{33}IN_4O_4Na$ *m/z* ($M+Na^+$) 819.2, found 819.0.



2.70

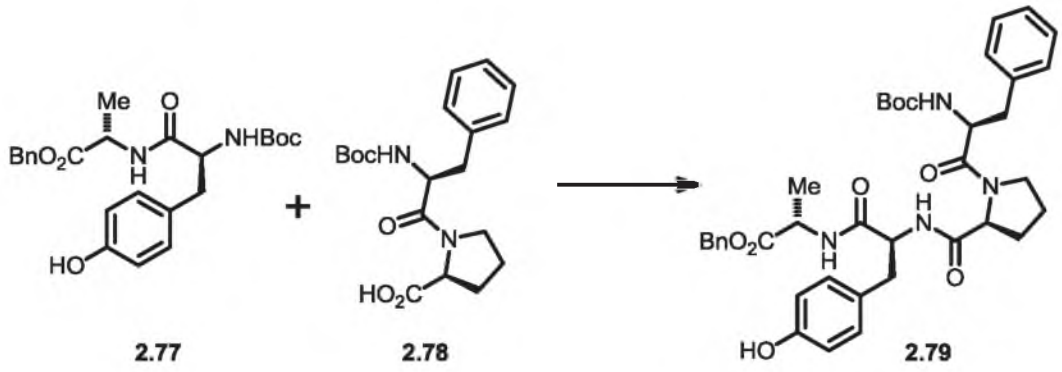
Preparation of (*S*)-benzyl 3-(1-((2*S*,2a^1*R*,4*S*,5a*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-benzyl-1,3-dioxo-2,2a^1,3,4,5,5a-hexahydro-1*H*-2a,9b-diazacyclopenta[*jk*]fluoren-5a-yl)-1H-indol-3-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (2.70). To a slurry of Zn dust (0.0315 g, 0.481 mmol) in *N,N*-dimethylacetamide (3 mL, degassed using the freeze-pump-thaw method) was added 1,2-diiodoethane (0.007 g, 0.02 mmol) and TMSCl (1.5 μL, 0.012 mmol). The mixture was sonicated for 0.5 h followed by the addition of L-serine derived iodide (0.126 g, 0.312 mmol) and sonicated for an additional 0.5 h. To the resulting zincate **2.67** was added Pd_2dba_3 (0.016 g, 0.018 mmol), P(*o*-tol)$_3$ (0.065 g, 0.21 mmol), CuBr·DMS (0.002 g, 0.009 mmol), followed by **2.69** (0.142 g, 0.178 mmol) in DMA (3 mL) and the mixture was sonicated for 2 h at a temperature that ranged from 22-38 °C. The resulting

reaction mixture was then diluted with CH_2Cl_2 (100 mL) and the reaction was quenched with a 1:1 mixture of water and brine (20 mL). After separation the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (25% EtOAc:hexanes) afforded 0.125 g (74%) of **2.70** as a colorless glass and 0.0140 g (12%) of recovered **2.53**. **2.70**: R_f 0.25 (33% EtOAc:hexanes); $[\alpha]_D$ = −56.5° (*c* = 0.670, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.36-7.27 (m, 4H), 7.23-7.19 (m, 7H), 7.11 (t, *J* = 7.4 Hz, 2H), 7.06-6.98 (m, 3H), 6.85 (dt, *J* = 8.3, 1.0 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.22 (d, *J* = 8.4 Hz, 1H), 6.16 (d, *J* = 3.8 Hz, 1H), 5.53 (s, 1H), 5.50 (d, *J* = 8.1 Hz, 1H), 5.19 (d, *J* = 12.5 Hz, 1H), 5.17 (dd, *J* = 5.5, 5.5 Hz, 1H), 5.05 (d, *J* = 12.4 Hz, 1H), 4.78 (dd, *J* = 13.1, 5.2 Hz, 1H), 4.43-4.38 (m, 3H), 4.22 (dd, *J* = 7.0, 7.0 Hz, 1H), 3.62 (d, *J* = 14.8 Hz, 1H), 3.38 (broad s, 2H), 3.28 (dd, *J* = 13.9, 5.5 Hz, 1H), 3.24 (dd, *J* = 14.2, 5.3 Hz, 1H), 1.97 (dd, *J* = 13.2, 13.2 Hz, 1 H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 170.4, 167.2, 156.1, 155.2, 143.7, 143.4, 141.3, 141.3, 137.7, 135.4, 134.9, 134.4, 130.5, 129.2, 128.6, 128.4, 128.2, 128.1, 127.8, 127.6, 127.1, 126.4, 125.1, 125.1, 123.8, 122.2, 120.1, 120.0, 119.6, 114.9, 111.0, 110.9, 81.7, 79.6, 67.5, 66.9, 65.2, 65.2, 54.4, 48.6, 47.0, 37.5, 36.4, 28.3, 27.9; IR (neat) 3361, 2976, 1715, 1682, 1485, 1457, 1345, 1294, 1219, 1167, 1060 cm^{-1}; LRMS (ESI) calcd for $C_{58}H_{53}N_5O_8Na$ *m/z* ($M+Na^+$) 970.4, found 970.4.



2.75 **2.76** **2.77**

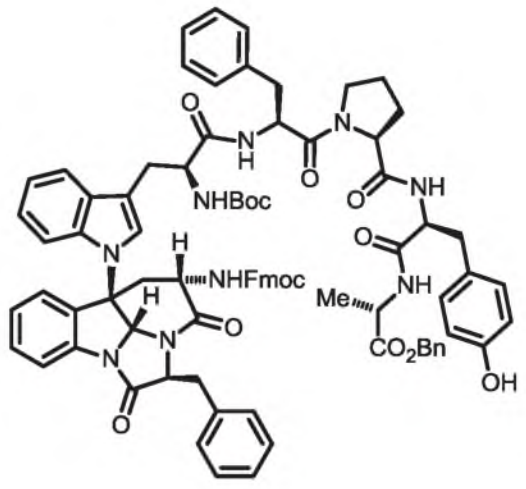
Preparation of (*S*)-benzyl 2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)propanoate (2.77). To a solution of acid **2.76** (0.385 g, 1.37 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added $HOBt{\cdot}H_2O$ (0.241 g, 1.78 mmol), DCC (0.311 g, 1.51 mmol), Et_3N (0.38 mL, 2.7 mmol), and 4Å molecular sieves. The resulting mixture was stirred for 0.5 h and then a solution of amine **2.75** (0.200 g, 0.684 mmol) in CH_2Cl_2 (5 mL) was added at once. The resulting mixture was allowed to warm to rt over 4 h, after which it was diluted with CH_2Cl_2 (100 mL). The reaction was quenched with citric acid (5% aq, 20 mL) and the organic phase was washed with sat. $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (30-40% EtOAc:hexanes) afforded 0.207 g (68%) of **2.77** as a colorless oil. **2.77**: R_f 0.25 (50% EtOAc:hexanes); $[\alpha]_D$ = +2.9° (*c* = 0.552, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, *c* = 0.0553 g/mL) δ 7.37-7.30 (m, 5H), 6.99 (d, *J* = 8.2 Hz, 2H), 6.96 (bs, 1H), 6.71 (d, *J* = 8.5 Hz, 2H), 6.65 (broad d, *J* = 6.9 Hz, 1H), 5.14 (s, 3H), 4.54 (broad s, 1H), 4.33 (broad s, 1H), 2.94 (d, *J* = 5.5 Hz, 2H), 1.40 (s, 9H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, *c* = 0.0553 g/mL) δ 172.3, 171.3, 155.6, 155.3, 135.2, 130.4, 128.6, 128.4, 128.1, 127.6, 115.6, 80.4, 67.2, 55.7, 48.2, 37.6, 33.8, 28.2, 18.2; IR (neat) 3308 (broad), 2980, 2935, 1742, 1661, 1517, 1453, 1368, 1248, 1163, 1050 cm^{-1}; LRMS (ESI) calcd for $C_{24}H_{30}N_2O_6Na$ *m/z* ($M+Na^+$) 465.2, found 465.2.



2.77 2.78 2.79

Preparation of (*S*)-benzyl 2-((*S*)-2-((*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoyl)pyrrolidine-2-carboxamido)-3-(4-hydroxyphenyl)propanamido)propanoate (2.79). To a solution of **2.77** (0.722 g, 1.58 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL) and allowed to stir until the starting material had been consumed (TLC, ~1 h). The mixture was concentrated under vacuum. In a separate vessel, to a solution of acid **2.78** (0.658 g, 1.82 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added HOBt·H_2O (0.344 g, 2.54 mmol), EDC·HCl (0.418 g, 2.18 mmol), Et*i*Pr_2 (0.60 mL, 3.6 mmol), and 4Å molecular sieves. The resulting mixture was stirred for 0.5 h and to this was added a solution of the TFA salt from **2.77** in THF (5 mL). The reaction mixture was allowed to warm to rt over 4 h after which it was diluted with CH_2Cl_2 (100 mL). The reaction was quenched with citric acid (5% aq, 20 mL) and the organic phase was washed with sat. $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (50-80% EtOAc:hexanes) afforded 0.651 g (60%) of **2.79** as a white solid. **2.79**: mp = 154-156°C, uncorrected; R_f 0.39 (80% EtOAc:hexanes); $[\alpha]_D$ = −39.1 (*c* = 0.094, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, *c* = 0.0638 g/mL) δ (1.5:1.0 mix of rotamers) 8.32 (s, 1H), 7.85 (d, *J* = 7.0 Hz, 1H), 7.44 (s, 0.73H), 7.40-7.18 (m, 24.5H), 7.04-6.96 (m, 4.8H), 6.86-6.80 (m, 3.5H), 6.76-6.70 (m,

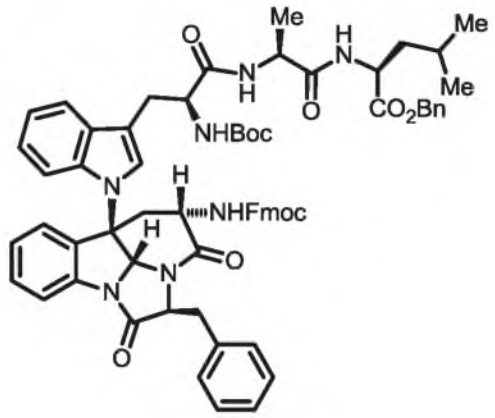
2.8H), 5.35 (d, J = 5.5 Hz, 1.2H), 5.30(d, J = 8.5Hz, 0.9H), 5.25-5.12 (m, 4.4H), 4.66-4.47 (m, 5.4H), 4.40 (dd, J = 8.0, 4.0 Hz, 1H), 4.35-4.29 (m, 1.3H), 3.58 (dd, J = 16.5, 7.0 Hz, 0.9H), 3.52 (d, J = 7.0 Hz, 1.2H), 3.34-3.27 (m, 1.2H), 3.22 (dd, J = 14.5, 5.0 Hz, 1.3H), 3.16-3.04 (m, 3H), 3.02-2.82 (m. 6.7H), 2.11 (s, 1.2H), 1.98-1.72 (m, 4.2H), 1.40-1.30 (m, 25H); ^{13}C NMR (125 MHz, $CDCl_3$, c = 0.0638 g/mL) δ mix of rotamers (1.5:1.0) 172.8, 172.3, 172.2, 172.0, 171.2, 171.1, 170.4, 170.4, 170.2, 156.6, 156.0, 155.7, 155.2, 136.2, 135.4, 134.9, 130.3, 129.8, 129.4, 129.0, 128.6, 128.6, 128.5, 128.4, 128.3, 128.1, 128.1, 128.0, 127.7, 127.6, 127.0, 115.5, 80.9, 80.0, 67.1, 67.1, 60.8, 60.6, 57.1, 54.6, 54.5, 53.4, 48.3, 48.0, 47.4, 46.7, 46.4, 38.8, 38.5, 36.7, 35.6, 32.8, 30.3, 28.3, 28.2, 24.8, 21.1, 18.5, 18.0; IR (neat) 3301 (broad), 2979, 1740, 1642, 1517, 1451, 1368, 1251, 1164, 1054 cm^{-1}; LRMS (ESI) calcd for $C_{38}H_{46}N_4O_8Na$ m/z ($M+Na^+$) 709.3, found 709.5.



2.71

Preparation of (*S*)-benzyl 2-((*S*)-2-((*S*)-1-((*S*)-2-((*S*)-3-(1-((2*S*,2a^1*R*,4*S*,5a*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-benzyl-1,3-dioxo-2,2a^1,3,4,5,5a-hexahydro-

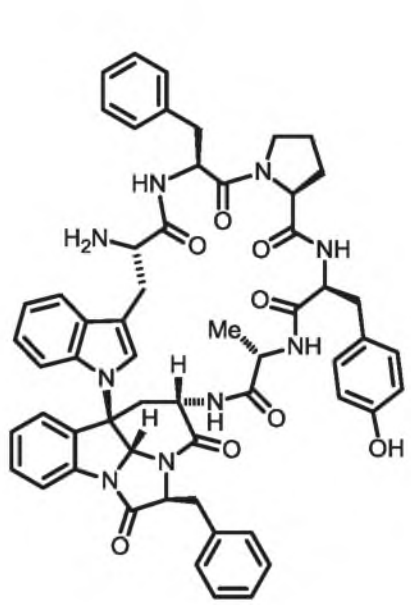
1*H*-2a,9b-diazacyclopenta[*jk*]fluoren-5a-yl)-1*H*-indol-3-yl)-2-((*tert*-butoxycarbonyl)amino)propanamido)-3-phenylpropanoyl)pyrrolidine-2-carboxamido)-3-(4-hydroxyphenyl)propanamido)propanoate (2.71). To a solution of **2.79** (0.105 g, 0.153 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL). The resulting mixture was stirred until the starting material was consumed (TLC, ~2 h). The reaction mixture was concentrated to provide **2.73** (0.107g, 0.153 mmol) as an oil. To a solution of **2.70** (0.058 g, 0.061 mmol) in THF (1.5 mL) and EtOH (1.5 mL) at 0 °C was added 10% Pd/C (~50% H_2O, 0.058 g). The resulting mixture at 0 °C was stirred under H_2 (1 atm) until the starting material was consumed (TLC) after which the mixture was diluted with EtOAc (5 mL) and filtered through a plug of celite. The filtrate was concentrated and the resulting residue taken up in CH_2Cl_2 (3 mL) and cooled to 0 °C. To this was added HOBt·H_2O (0.021 g, 0.15 mmol), EDC·HCl (0.023 g, 0.12 mmol), Et*i*Pr_2 (0.32 mL, 0.18 mmol), and 4Å molecular sieves. The resulting mixture was stirred for 0.5 h and then a solution of **2.73** (0.107 g, 0.153 mmol) in THF (3 mL) was added at once. The reaction mixture was allowed to warm to rt over 6 h and was then diluted with CH_2Cl_2 (100 mL). The reaction was quenched with citric acid (5% aq, 20 mL) and the organic phase was washed with sat. $NaHCO_3$ (aq, 20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (60% EtOAc:hexanes) afforded 0.052 g (60%) of **2.71** as a milky glass. R_f 0.31 (66% EtOAc:hexanes); LRMS (ESI) calcd for $C_{84}H_{83}N_9O_{13}Na$ *m/z* ($M+Na^+$) 1448.6, found 1448.7.



2.72

Preparation of (6*S*,9*S*,12*S*)-benzyl 6-((1-((2*S*,2a^1*R*,4*S*,5a*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-benzyl-1,3-dioxo-2,2a^1,3,4,5,5a-hexahydro-1*H*-2a,9b-diazacyclopenta[*jk*]fluoren-5a-yl)-1*H*-indol-3-yl)methyl)-12-isobutyl-2,2,9-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (2.72). To a solution of **2.70** (0.106 g, 0.111 mmol) in THF (3 mL) and EtOH (3 mL) at 0 °C was added 10% Pd/C (~50% H_2O, 0.106 g). The resulting mixture was stirred under H_2 (1 atm) until the starting material had been consumed (TLC) after which the reaction mixture was diluted with EtOAc (10 mL) and filtered through a plug of celite. The filtrate was concentrated, the resulting residue taken up in CH_2Cl_2 (5 mL) and cooled to 0 °C. To this was added HOBt·H_2O (0.038 g, 0.28 mmol), EDC·HCl (0.043 g, 0.22 mmol), Et*i*Pr$_2$ (0.58 mL, 0.33 mmol), and 4Å molecular sieves. After 0.5 h a solution of **2.74** (0.113 g, 0.279 mmol) in CH_2Cl_2 was added at once. The reaction mixture was allowed to warm to rt over 4 h and then was diluted with CH_2Cl_2 (100 mL). The reaction was quenched with citric acid (5% aq, 20 mL). The organic phase was washed with sat. $NaHCO_3$ (aq, 20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (33% EtOAc:hexanes) afforded 0.0890 g (71%) of **2.72** as a colorless glass. **2.72**: R_f 0.10 (33%

EtOAc:hexanes); $[\alpha]_D = -104.2°$ (c = 0.910, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.82-7.74 (partially obscured m, 1H), 7.77 (d, J = 7.5 Hz, 2H), 7.68 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 7.2 Hz, 1H), 7.68-7.64 (partially obscured m, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2 H), 7.30-7.22 (m, 7H), 7.20 (broad d, J = 7.3 Hz, 3H), 7.12 (t, J = 7.5 Hz, 2H), 7.01 (t, J = 7.7 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 6.78 (t, J = 7.3, 1H), 6.73-6.67 (m, 1H), 6.29 (broad s, 1H), 6.17 (d, J = 8.4 Hz, 1H), 5.56-5.50 (m, 1H), 5.40 (s, 1H), 5.15 (dd, J = 5.1, 5.1 Hz, 1H), 5.07 (dd, J = 12.1, 12.1 Hz, 1H), 5.04 (dd, J = 12.1, 12.1 Hz, 1H), 4.82 (broad s, 1H), 4.64 (broad s, 1H), 4.52 (d, J = 12.8 Hz, 1H), 4.42-4.28 (m, 4H), 3.89 (d, J = 14.5 Hz, 1H), 3.33 (dd, J = 15.3, 9.2 Hz, 1H), 3.30-3.21 (m, 2H), 3.10 (d, J = 12.8 Hz, 1H), 1.97 (dd, J = 13.8, 13.8 Hz, 1H), 1.43-1.26 (partially obscured m, 2H), 1.35 (s, 9H), 1.16 (s, 3H), 0.61 (s, 3H), 0.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 172.1, 171.6, 170.6, 167.0, 156.7, 155.2, 143.8, 143.3, 141.3, 141.2, 137.8, 135.3, 134.9, 134.3, 130.3, 129.9, 129.2, 128.6, 128.5, 128.3, 128.2, 127.8, 127.6, 127.2, 127.1, 126.4, 125.2, 125.1, 124.9, 124.1, 122.2, 120.0, 119.8, 119.2, 114.6, 110.9, 110.7, 82.0, 79.7, 67.8, 66.9, 65.3, 65.0, 53.2, 51.0, 48.9, 48.7, 47.0, 40.7, 37.5, 36.4, 28.7, 28.2, 24.5, 22.4, 21.4, 17.1; IR (neat); 3342, 2960, 1712, 1677, 1503, 1456, 1367, 1222, 1164, 1083 cm^{-1}; LRMS (ESI) calcd for $C_{67}H_{69}N_7O_{10}Na$ m/z ($M+Na^+$) 1154.5, found 1154.5.



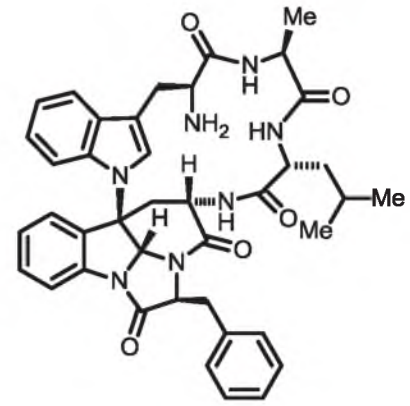
kapakahine E (**2.4**)

Preparation of Kapakahine E (2.4). To a solution of **2.71** (0.040 g, 0.028 mmol) in EtOH (2 mL) and EtOAc (1 mL) at rt was added 10% Pd/C (~50% H_2O, 0.080 g). The resulting mixture was stirred under H_2 (1 atm) until the starting material was consumed (TLC) after which ammonium formate (0.026 g, 0.420 mmol) was added in three portions over 1 h. After the starting material had been consumed (TLC) the reaction mixture was diluted with EtOAc (3 mL) and EtOH (3 mL). The insolubles were removed by centrifugation, rinsing with EtOH, and concentration. The resulting residue was purified by prep TLC (60% EtOAc:hexanes, desired material extracted from SiO_2 using MeOH). To the resulting residue in CH_2Cl_2 (9.3 mL) and DMF (4.7 mL) was added HATU (0.053 g, 0.14 mmol), Et*i*Pr$_2$ (0.024 mL, 0.14 mmol), and 4Å molecular sieves. The reaction mixture was allowed to stir at rt for 1.5 d after which it was diluted with CH_2Cl_2 (80 mL). The reaction was quenched with a mixture of 5% citric acid:brine (40 mL, (1:1)) and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were concentrated. Flash chromatography (80% EtOAc:hexanes)

afforded 0.015 g (50%) of ***N*-Boc-Kapakahine E** as a colorless glass. ***N*-Boc-Kapakahine E**: R_f 0.28 (80% EtOAc:hexanes); $[\alpha]_D = -91.8°$ (*c* = 0.114, CH_3OH); ^1H NMR (500 MHz, CD_3CN) δ 7.83 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.44 (broad d, *J* = 5.8 Hz, 1H), 7.39 (t, *J* = 8.4 Hz, 3H), 7.36-7.30 (m, 4H), 7.23 (d, *J* = 7.3 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.01-6.94 (m, 4H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.69 (bs, 1H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.53 (d, *J* = 7.4 Hz, 1H), 6.30 (d, *J* = 8.5 Hz, 1H), 6.05 (d, *J* = 6.9 Hz, 1H), 5.67 (s, 1H), 4.98-4.94 (m, 2H), 4.80-4.71 (m, 2H), 4.70-4.65 (m, 1H), 4.51-4.49 (m, 1H), 4.35 (dd, *J* = 11.5, 6.5 Hz, 1H), 4.00-3.94 (m, 1H), 3.88 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.75 (dd, *J* = 16.5, 8.5 Hz, 1H), 3.63 (d, *J* = 15.0 Hz, 1H), 3.33 (dd, *J* = 15.0, 7.0 Hz, 1H), 3.22 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.13 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.10-3.03 (m, 2H), 2.98 (dd, *J* = 14.5, 5.0 Hz, 1H), 2.90 (dd, *J* = 14.0, 3.5 Hz, 1H), 2.56 (dd, *J* = 14.0, 11.0 Hz, 1H), 2.38 (dd, *J* = 14.5, 14.5 Hz, 1H), 2.12-2.00 (m 3H), 1.73-1.64 (m, 1H), 1.40 (s, 9H), 1.36 (d, *J* = 6.5 Hz, 3H) ; ^{13}C NMR (125 MHz, CD_3CN) δ 175.0, 173.5, 173.3, 172.9, 172.0, 171.3, 168.9, 157.4, 156.0, 140.5, 137.9, 137.5, 136.5, 135.8, 132.1, 131.7, 131.6, 130.9, 130.6, 130.1, 129.7, 128.9, 128.4, 128.4, 127.1, 126.5, 124.2, 123.1, 121.0, 120.6, 116.6, 115.9, 112.3, 111.4, 83.0, 80.2, 67.7, 66.1, 64.7, 55.8, 55.2, 54.4, 49.3, 49.3, 48.7, 38.4, 38.2, 37.5, 36.1, 30.5, 28.9, 26.5, 18.2; IR (neat) 3410, 3333, 2924, 1671, 1521, 1485, 1458, 1368, 1165 cm^{-1}; LRMS (ESI) calcd for $C_{62}H_{65}N_9O_{10}Na$ *m/z* ($M+Na^+$) 1118.5, found 1118.5.

To a solution of **N-Boc-Kapakahine E** (0.015 g, 0.014 mmol) in CH_2Cl_2 (3 mL) at rt was added freshly distilled TFA (0.3 mL). Toluene (3 mL) was added to the resulting after 1.5 h and the resulting mixture was concentrated to give 15 mg of **Kapakahine E**

(100% yield) as a yellow TFA salt. **Kapakahine E**: yellow solid; R_f 0.33 (50% CH_3CN:H_2O, 0.1% TFA on C_{18} reverse phase silica gel); $[\alpha]_D$ = −82.8° (*c* = 0.288, CH_3OH); ^1H NMR (500 MHz, CD_3CN) δ 7.84 (bs, 1H), 7.78 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.43-7.37 (m, 4H), 7.34 (t, *J* = 7.0 Hz, 1H), 7.34-7.31 (partially obscured m, 1 H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 7.4 Hz, 2H), 7.16 (d, *J* = 7.0 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.12-7.06 (m, 2H), 7.05-6.98 (partially obscured m, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 7.4 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 6.21 (d, *J* = 6.1 Hz, 1H), 5.74 (s, 1H), 4.97 (t, *J* = 5.8 Hz, 1H), 4.73 (ddd, *J* = 11.1, 4.4, 4.4 Hz, 1 H), 4.70-4.63 (m, 2H), 4.39 (bs, 1H), 4.31 (dd, *J* = 12.4, 6.4 Hz, 1H), 3.99-3.93 (m, 1H), 3.90 (t, *J* = 8.1 Hz, 1H), 3.77 (dd, *J* = 17.1, 7.1 Hz, 1H), 3.67-3.51 (m, 2H), 3.50-3.43 (m, 2H), 3.23 (dd, *J* = 14.1, 5.4 Hz, 1H), 3.14 (dd, *J* = 13.7, 4.7 Hz, 1H), 3.10-2.99 (m, 2H), 2.99 (dd, *J* = 15.5, 4.5 Hz, 1H), 2.72 (dd, *J* = 14.6, 10.7 Hz, 1H), 2.47 (dd, *J* = 15.1, 13.4 Hz, 1H), 2.14-1.99 (m, 2H), 1.75-1.66 (m, 1H), 1.58-1.50 (m, 1H), 1.37 (d, *J* = 7.0 Hz, 3H) ; ^{13}C NMR (125 MHz, CD_3CN) δ 174.5, 173.8, 173.1, 172.7, 171.1, 169.0, 168.7, 157.1, 140.3, 137.4, 137.2, 135.9, 135.8, 131.5, 131.3, 130.6, 130.2, 130.0, 129.9, 129.4, 129.3, 128.5, 128.3, 128.2, 127.1, 126.9, 126.3, 124.1, 123.2, 121.4, 120.0, 116.3, 115.6, 112.2, 107.4, 82.4, 68.0, 65.7, 64.5, 56.2, 54.9, 54.7, 49.1, 48.6, 48.3, 37.9, 37.3, 37.2, 35.7, 30.4, 30.1, 26.2, 17.9; IR (neat) 3369, 1731, 1681, 1455, 1173 cm^{-1}; HRMS (ESI) calcd for $C_{57}H_{58}N_9O_8$ ($M+H^+$) *m/z* 996.4408, found 996.4396.



kapakahine F (**2.5**)

Preparation of Kapakahine F (2.5). To a solution of **2.72** (0.045 g, 0.040 mmol) in EtOH:EtOAc (4 mL, (2:1)) at rt was added 10% Pd/C (~50% H_2O, 0.090 g). The resulting mixture was stirred under H_2 (1 atm) until the starting material was consumed (TLC) after which ammonium formate (0.038 g, 0.600 mmol) was added in three portions over 1 h. The mixture was diluted with EtOAc (3 mL) and EtOH (3 mL) and the insolubles were removed by centrifugation. Following concentration, the resulting residue was dissolved in CH_2Cl_2:DMF (20 mL, (2:1)). To this was added HATU (0.076 g, 0.20 mmol), Et*i*Pr_2 (0.035 mL, 0.20 mmol), and 4Å molecular sieves. After stirring at rt for 1.5 d the resulting mixture was diluted with CH_2Cl_2 (80 mL) and the reaction was quenched with a 5% citric acid:brine solution (40 mL, (1:1)). The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL), and the organic extracts were combined and concentrated. Flash chromatography (75% EtOAc:hexanes) afforded 0.025 g (78%) of **N-Boc-Kapakahine F** as a colorless glass. **N-Boc-Kapakahine F**: R_f 0.22 (75% EtOAc:hexanes); $[\alpha]_D = -178.6°$ (c = 0.104, CH_3OH); ^1H NMR (500 MHz, CD_3CN) δ 7.59 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 7.8 Hz, 2H), 7.27 (d, J = 7.3 Hz, 2H), 7.26 (s, 1H), 7.20 (bs, 1H), 7.17 (t, J = 7.8 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H),

6.99 (t, J = 7.8 Hz, 1H), 6.98-6.90 (m, 2H), 6.81 (t, J = 7.9 Hz, 1H), 6.65 (broad d, J = 6.4 Hz, 1H), 6.31 (d, J = 8.3 Hz, 1H), 5.70 (s, 1H), 5.51 (broad d, J = 7.9 Hz, 1H), 4.96 (t, J = 5.8 Hz, 1H), 4.78 (dd, J = 12.2, 8.3 Hz, 1H), 4.44-4.30 (m, 3H), 3.38 (dd, J = 15.2, 8.3 Hz, 1H), 3.22 (dd, J = 14.2, 5.3 Hz, 1H), 3.14 (dd, J = 14.2, 5.9 Hz, 1H), 2.95 (d, J = 14.6 Hz, 1H), 2.84 (d, J = 14.7 Hz, 1H), 2.63 (t, J = 13.2 Hz, 1H), 1.70-1.50 (m, 3H), 1.41 (s, 9H), 1.38 (d, J = 7.8 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 174.9, 174.4, 173.1, 172.8, 169.1, 156.6, 140.6, 137.5, 135.6, 135.3, 132.2, 131.6, 130.9, 129.7, 128.5, 127.1, 126.8, 124.9, 122.9, 121.1, 120.2, 115.9, 112.2, 83.3, 80.5, 69.3, 65.6, 56.1, 53.5, 52.4, 49.2, 41.1, 39.3, 37.7, 28.9, 28.4, 26.1, 23.5, 22.8, 18.1; IR (neat) 3360, 1666, 1520, 1451, 1363, 1225, 1167 cm^{-1}; LRMS (ESI) calcd for $C_{45}H_{51}N_7O_7Na$ *m/z* ($M+Na^+$) 824.3, found 824.4.

To a solution of **N-Boc-Kapakahine F** (0.023 g, 0.029 mmol) in CH_2Cl_2 (5 mL) was added freshly distilled TFA (0.5 mL). Toluene (5 mL) was added after 1.5 h and the resulting mixture was concentrated to give **Kapakahine F** as a white TFA salt. **Kapakahine F**: $[\alpha]_D$ = −142.5° (c = 0.36, CH_3OH); ^{1}H NMR (500 MHz, (CD_3CN: CD_3OH:AcOH 200:100:1)) δ 8.26 (d, J = 7.8 Hz, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.60 (partially obscured broad s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.34 (t, J = 7.3 Hz, 1H), 7.24 (d, J = 7.3 Hz, 2H), 7.15 (s, 1H), 7.12 (t, J = 7.3 Hz, 2H), 7.04 (t, J = 7.6 Hz, 2H), 6.98 (t, J = 7.3 Hz, 1H), 6.86 (d, J = 7.4 Hz, 1H), 6.82 (t, J = 7.9 Hz, 1H), 6.28 (d, J = 8.3 Hz, 1H), 5.55 (s, 1H), 4.98 (dd, J = 5.4 Hz, 1H), 4.67 (dd, J = 12.8, 8.8 Hz, 1H), 4.59 (ddd, J = 15.2, 7.8, 7.8 Hz, 1H), 4.30 (dd, J = 3.2, 3.2 Hz, 1H), 4.18 (dd, J = 13.3, 7.0 Hz, 1H), 3.42 (d, J = 3.9 Hz, 2H), 3.22 (dd, J = 14.2, 4.9 Hz, 1H), 3.12 (dd, J = 14.5, 6.0 Hz, 1H), 2.96 (d, J = 14.6 Hz, 1H), 2.57 (dd, J = 14.6, 13.2 Hz, 1H),

1.70-1.60 (m, 3H), 1.42 (d, J = 7.5 Hz, 1H), 0.96 (d, J = 6.0 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, (CD_3CN: CD_3OH:AcOH 200:100:1)) δ 175.8, 174.2, 173.1, 169.6, 169.4, 140.6, 137.2, 135.5, 135.2, 132.1, 131.7, 130.8, 129.7, 128.5, 127.5, 127.0, 125.4, 123.3, 121.4, 119.8, 115.8, 112.3, 106.4, 83.5, 69.2, 65.7, 54.5, 54.4, 51.1, 49.9, 39.8, 39.0, 37.5, 26.0, 25.8, 23.3, 22.7, 17.8; IR (neat) 3287, 2924, 1674, 1484, 1455, 1292, 1201, 1134 cm^{-1}; LRMS (ESI) calcd for $C_{40}H_{44}N_7O_5$ *m/z* ($M+H^+$) 702.3, found 702.3.

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CHAPTER 3

TOWARD THE TOTAL SYNTHESIS OF CHETOMIN

Introduction

The class of natural products containing the epidithiodiketopiperazine moiety is a very diverse subset and includes the title compound chetomin (Figure 3.1-3.2).[1] Chetomin, isolated from *Chaetomium cocliodes* in 1944, represents one of the first C(3)-N(1′) heterodimeric indoline natural products to be isolated and was shown to have antibacterial properties. More recently it was shown to be an inhibitor of the binding of HIF-1α to p300, thus a disruptor of protein-protein interactions within tumors.[2a-i] The structure was originally proposed to be **3.1**, but was revised to **3.2** after extensive NMR evaluation (Figure 3.1).[2c,d]

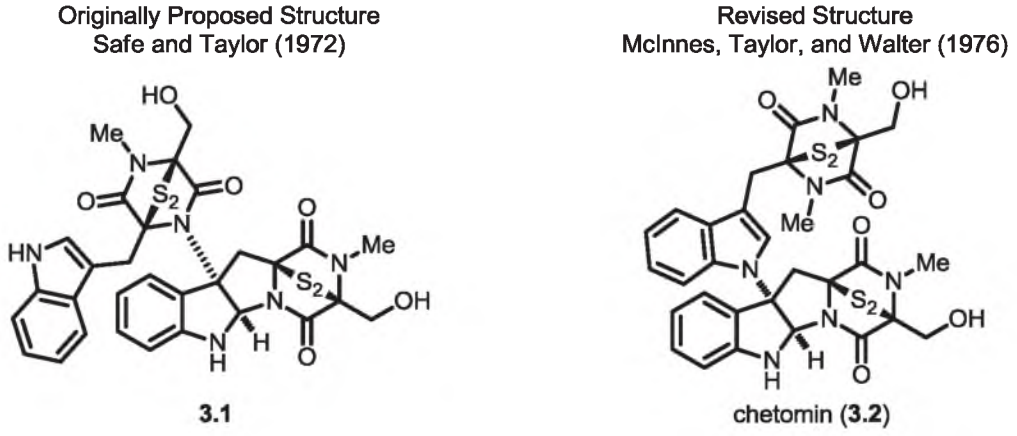


Figure 3.1. The Structure of Chetomin

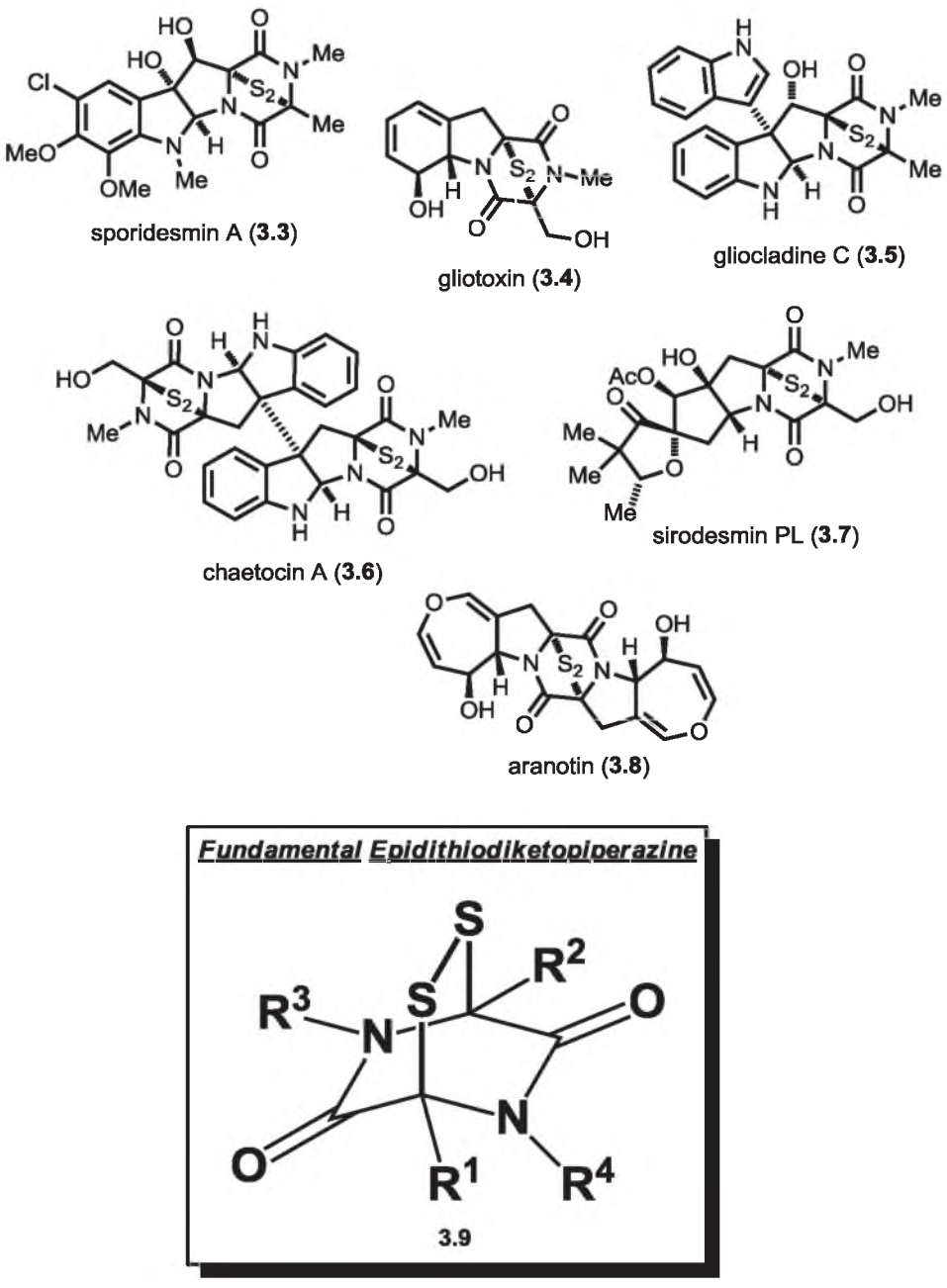


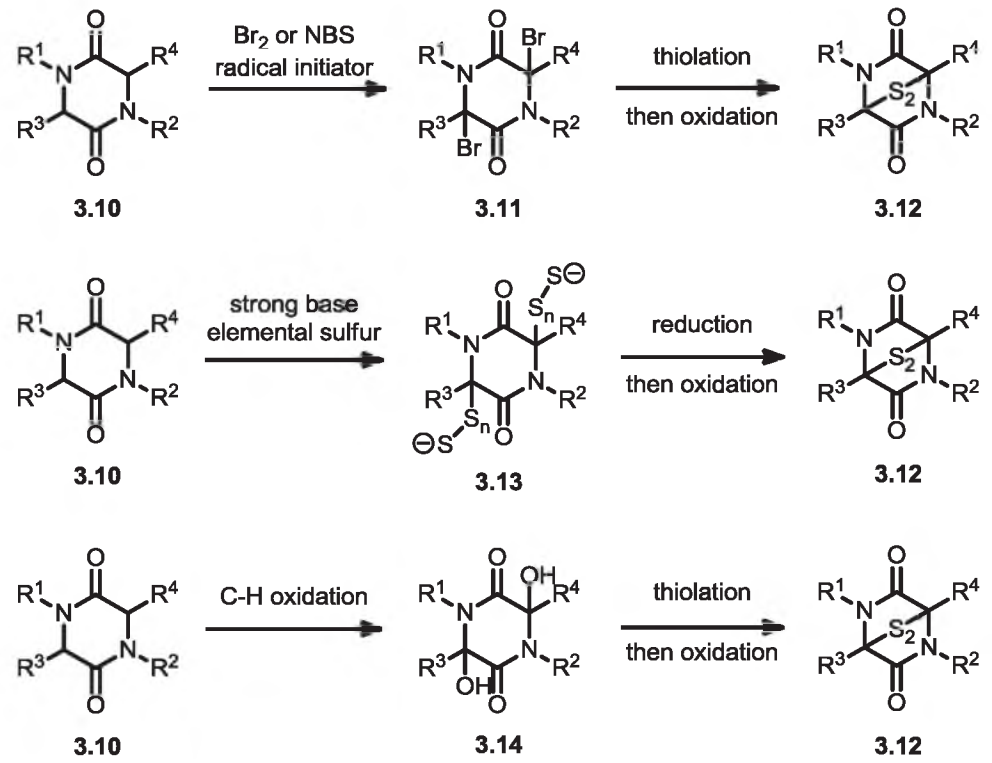
Figure 3.2. Representative Epidithiodiketopiperazine Natural Products

Previous Work

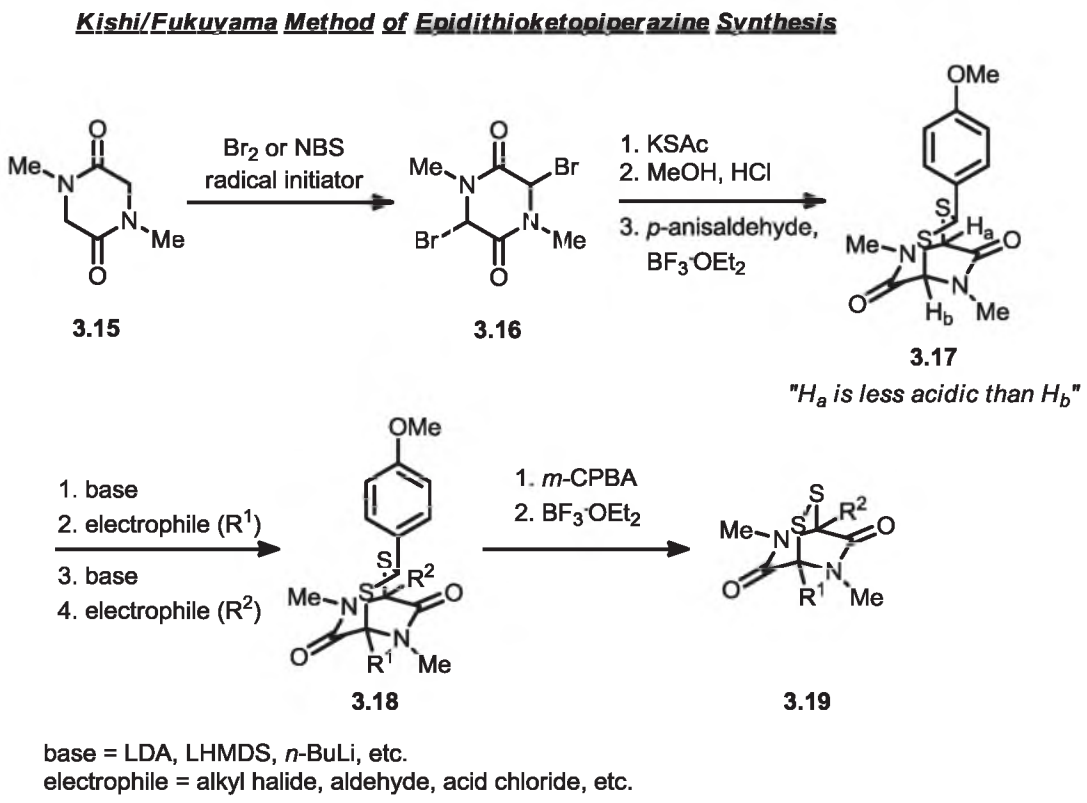
The epidithiodiketopiperazines represent a class of compounds that are notoriously difficult to synthesize and manipulate.[1g] Synthesis of epidithiodiketopiperazines from the parent diketopiperazine has been the premier method of their synthesis and the early methods that were developed came in the late 1960s and 1970s.[3] Later methods of the synthesis of epidithiodiketopiperazines relied on improvements to the previous methods or invention of new methods.[4] The most common methods are outlined in Scheme 3.1. The formation of the disulfide bridge usually represents an endpoint in the synthesis because disulfide bridges are generally unstable (vide supra). The following total syntheses give a representative view of the different approaches to epidithiodiketopiperazines.

Kishi and Fukuyama devised an ingenious approach toward installing the disulfide bridge by introducing a way to mask the disulfide with a protecting group, in this case anisaldehyde to afford a dithiane, that was acid and base stable and could be unmasked to give the disulfide with relative ease (Scheme 3.2). The deprotection step involved oxidation of the dithiane to the mono-sulfoxide and reacting this immediately with a lewis acid or strong protic acid. This methodology allowed them to complete a number of complex natural products containing the epidithiodiketopiperazine motif including sporidesmin A (Scheme 3.3).[3g-j]

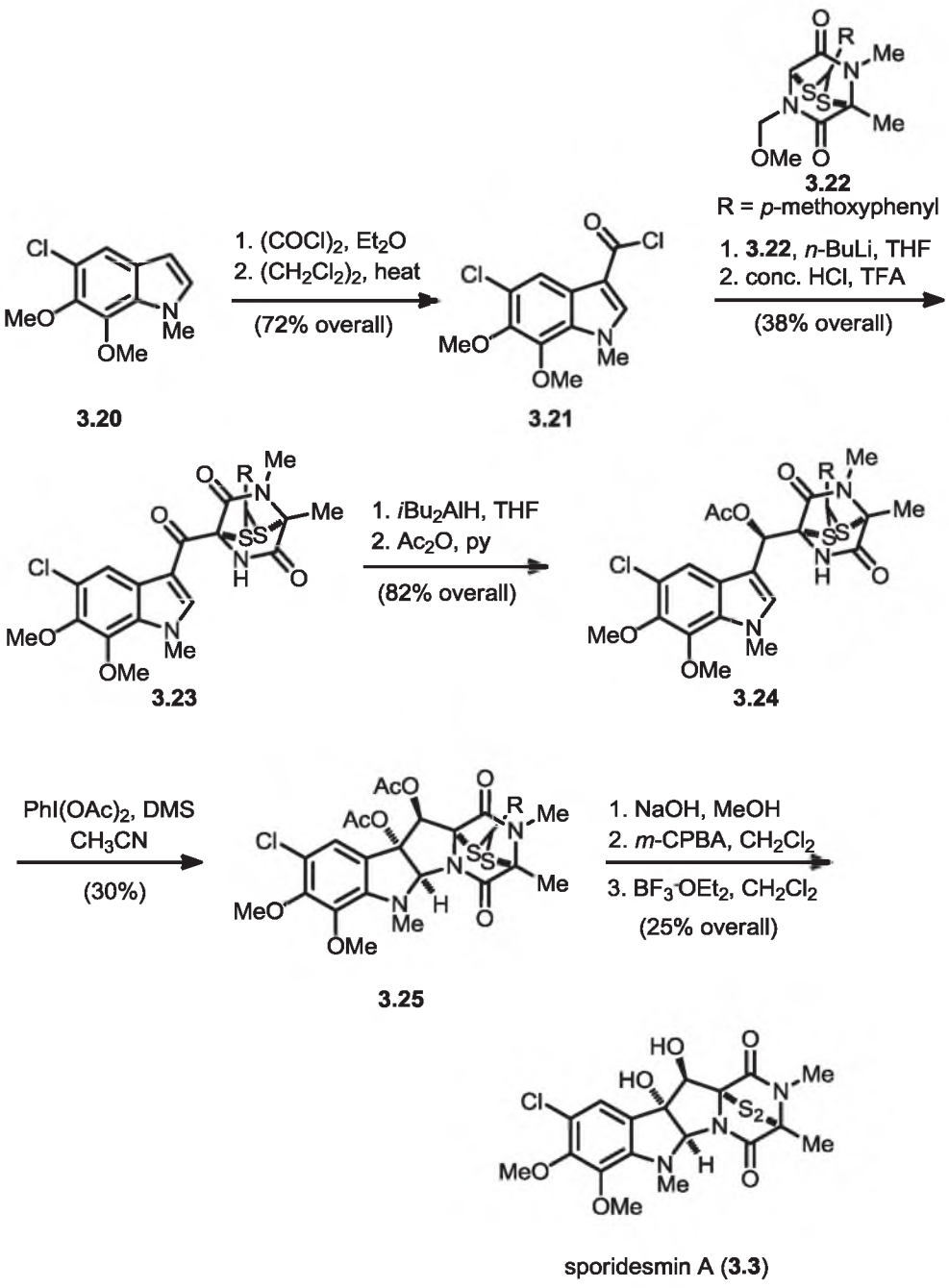
General Methods for Epidithiodiketopiperazine Synthesis from Diketopiperazines



Scheme 3.1. Synthesis of Epidithiodiketopiperazines from Diketopiperazines



Scheme 3.2. Kishi's Dithiane Synthesis

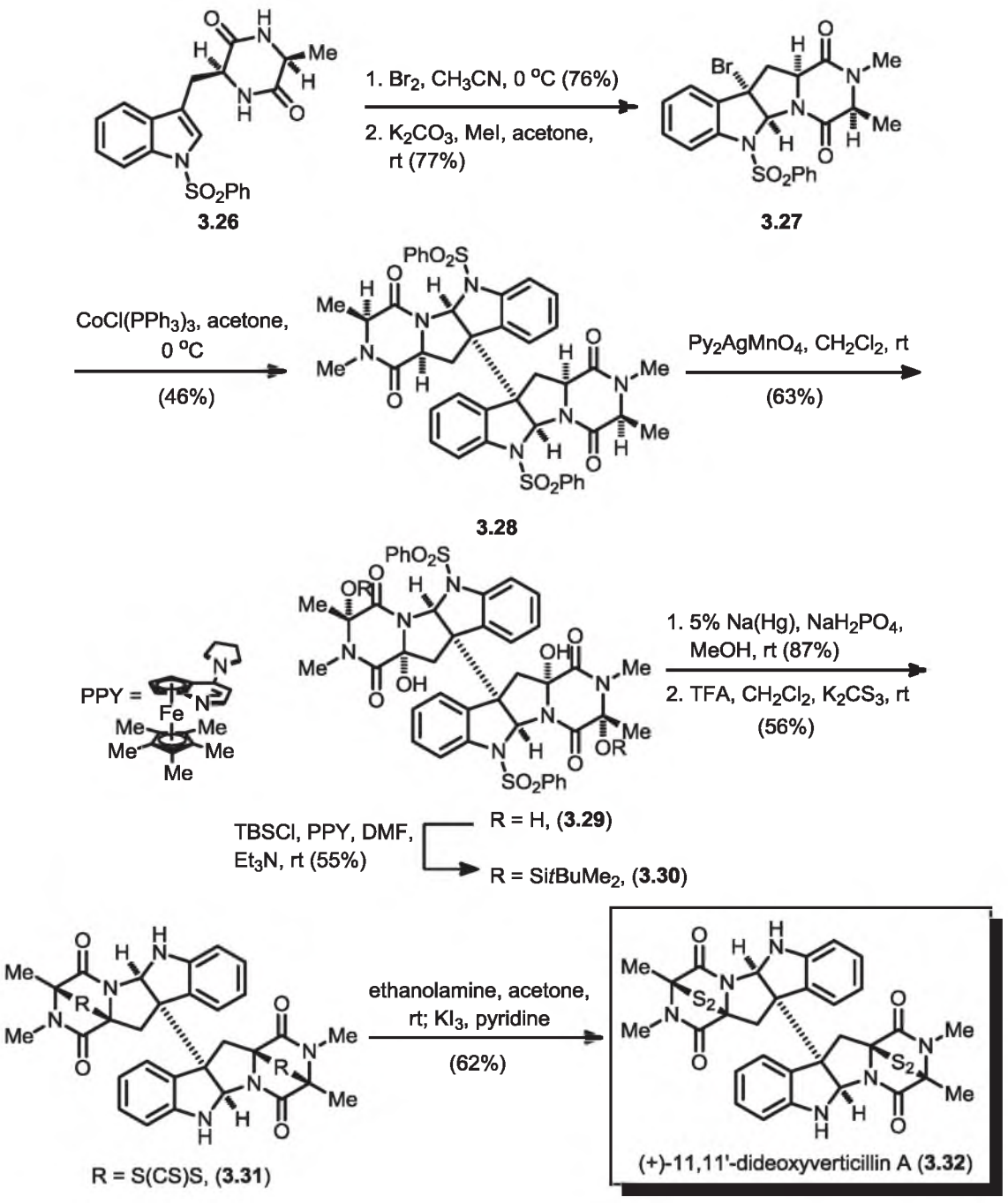


Scheme 3.3. Kishi's Total Synthesis of Sporidesmin A

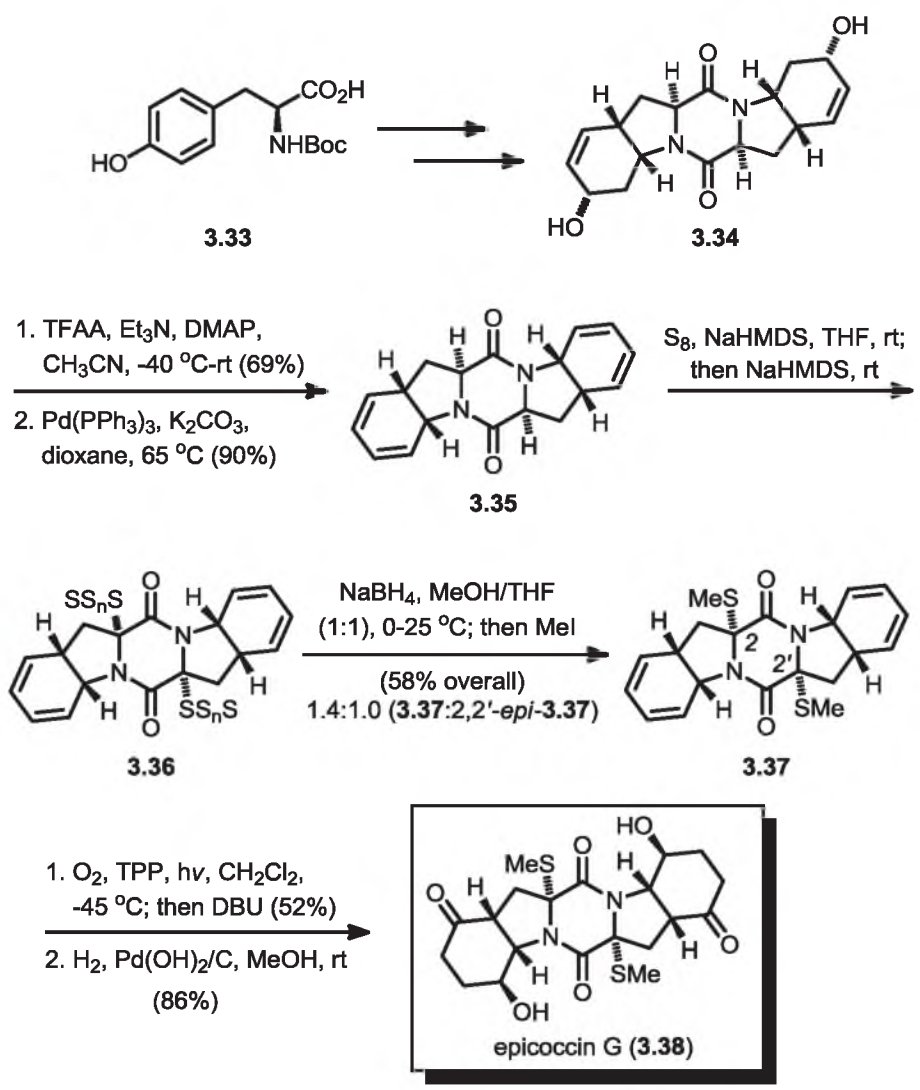
The Movassaghi group developed a very elegant protocol for the introduction of sulfur at the alpha position of the diketopiperazine which relied on selective C-H oxidation of the methine protons using a permanganate oxidant, followed by thiolation and oxidation. This methodology allowed them to complete a number of complex molecules including (+)-11,11′-dideoxyverticillin A and chaetocins A and C (Scheme 3.4).[4i,k] Key to this synthesis was the discovery of the ability of permanganate salts to smoothly oxidize diketopiperazines through a fast hydrogen atom abstraction/oxidation rebound mechanism.[5]

Nicolaou and coworkers completed a total synthesis of epicoccin G (Scheme 3.5).[4m] Their synthesis relied on trapping an enolate with electrophilic sulfur, in this case elemental sulfur, to give a bis-polysulfide similar to the Schmidt synthesis of epidithiodiketopiperazines. The polysulfide is reduced to the dithiol with sodium borohydride and either oxidized to the disulfide or converted into a bis-methylsulfide.

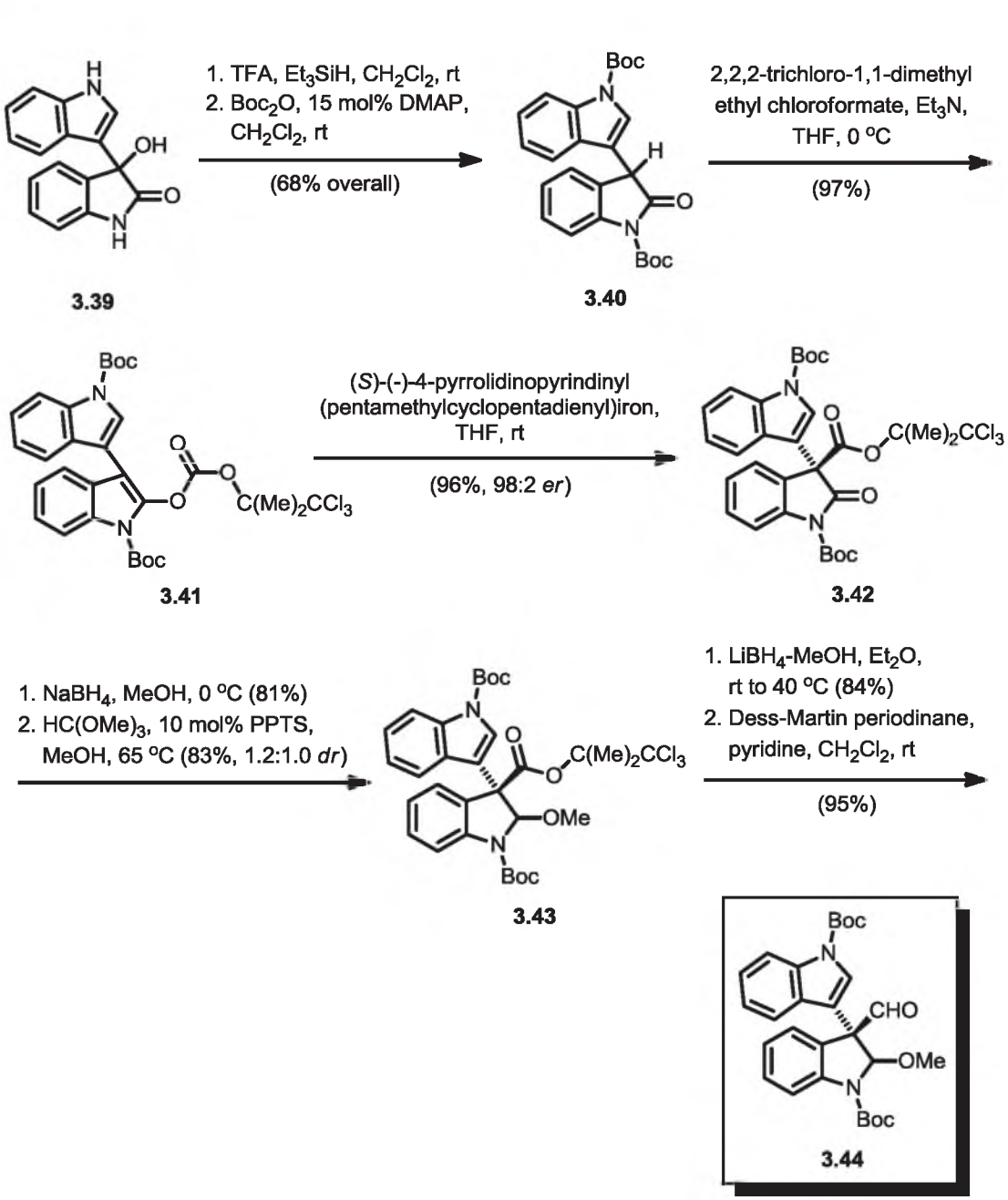
The Overman group elegantly completed a total synthesis of both gliocladin C and gliocladine C (Schemes 3.6 and 3.7). Starting from known indole dimer **3.39**, they rapidly constructed **3.42** using a desymmetrization process that involved carbonyl migration. Imide reduction and conversion of the ester to an aldehyde afforded **3.44** that was coupled to masked trioxopiperazine **3.45**. Lewis acid mediated cyclization gave trioxopiperazine **3.47**. Selective addition of MeMgCl to the trioxopiperazine gave a tertiary alcohol that could be converted to the disulfide natural product gliocladine C. Alternatively, **3.47** could also be converted to gliocladin C through protecting group removal.



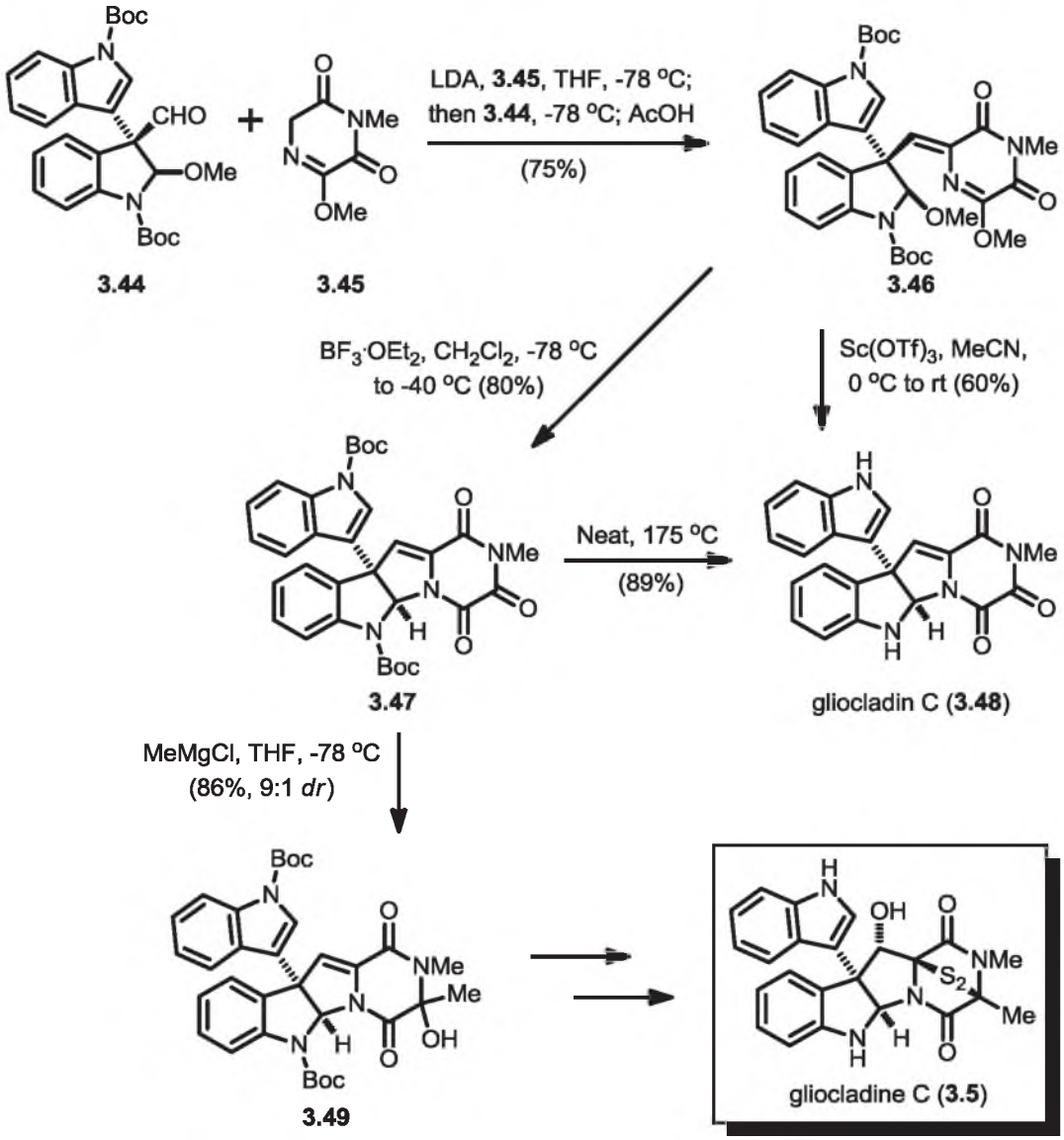
Scheme 3.4. Movassaghi's Total Synthesis of (+)-11,11′-Dideoxyverticillin A



Scheme 3.5. Nicolaou's Total Synthesis of Epicoccin G



Scheme 3.6. Overman's Synthesis of Indole Dimer **3.44**



Scheme 3.7. Overman's Total Syntheses of Gliocladin C and Gliocladine C

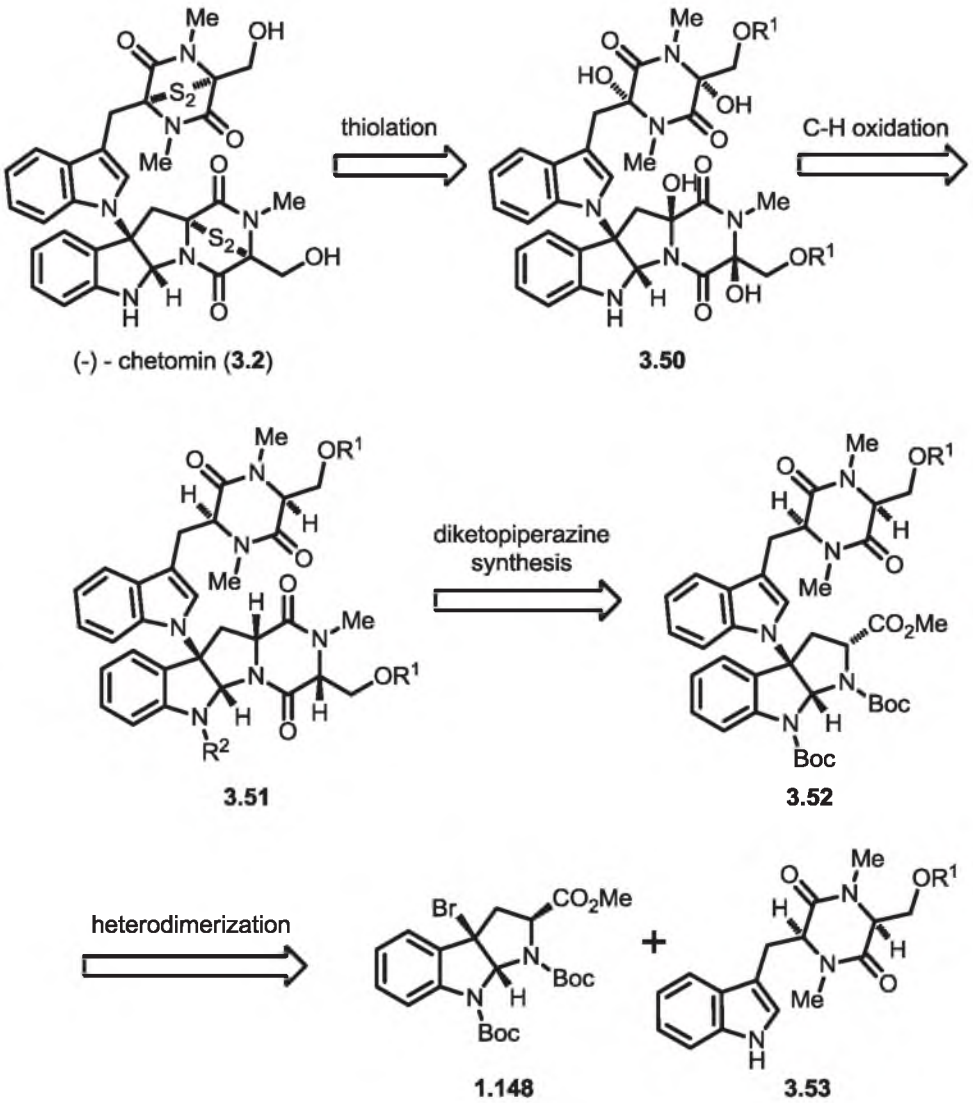
Retrosynthesis

Our retrosynthetic plan for the total synthesis of chetomin was devised to implement a direct oxidation of diketopiperazines to hydroxylated diketopiperazines that could then be converted to epidithiodiketopiperazines. From the retrosynthesis, the first disconnection was determined by the known instability of the disulfide bridges, so the introduction of the disulfide bridge was designed to come late in the synthesis (Scheme 3.8). The next disconnection was the introduction of the hydroxyl groups through the direct C-H oxidation of the bis-diketopiperazine **3.51**. The bis-diketopiperazine **3.51** could be synthesized by introduction of the pyrroloindoline fused diketopiperazine from **3.52** following the C(3)-N(1′) bond formation between bromopyrroloindoline **1.148** and tryptophan **3.53**.

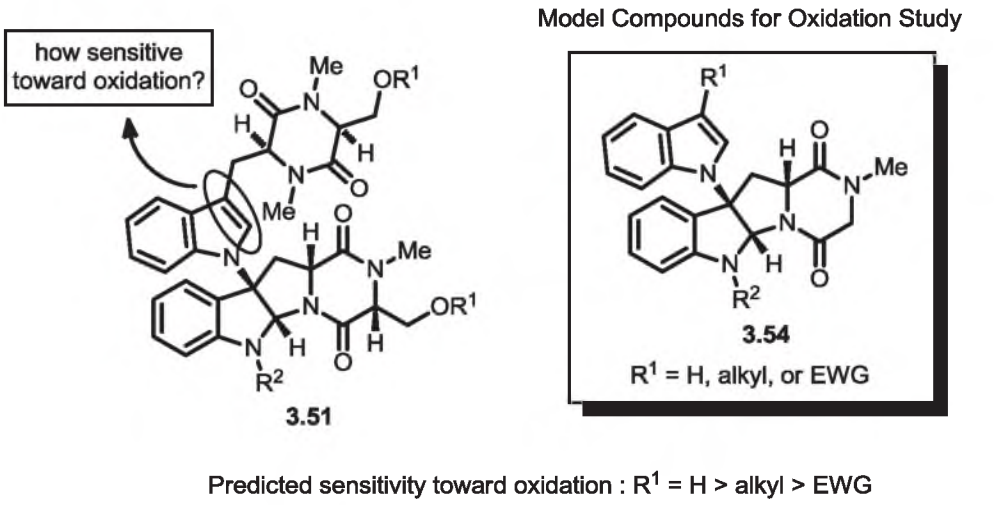
A potential problem with this synthetic route is that the stability of the substrate **3.51** toward the oxidative conditions required to give tetraol **3.50** is unknown. The indole-[2,3]-π double bond is quite sensitive to oxidants such as permanganate, chromium, mercury, and lead salts and could potentially give unwanted by-products. Therefore, a series of experiments were devised to test the sensitivity of the indole-[2,3]-π double bond toward oxidative conditions (Scheme 3.9). We hypothesized that an electron-withdrawing group at the C(3)-position of indole in **3.54** would be more stable toward oxidation than the parent indole.

Model Study

A model study was performed to test the spectrum of reactivity in the indole series containing a simple pyrroloindoline fused diketopiperazine toward oxidative conditions



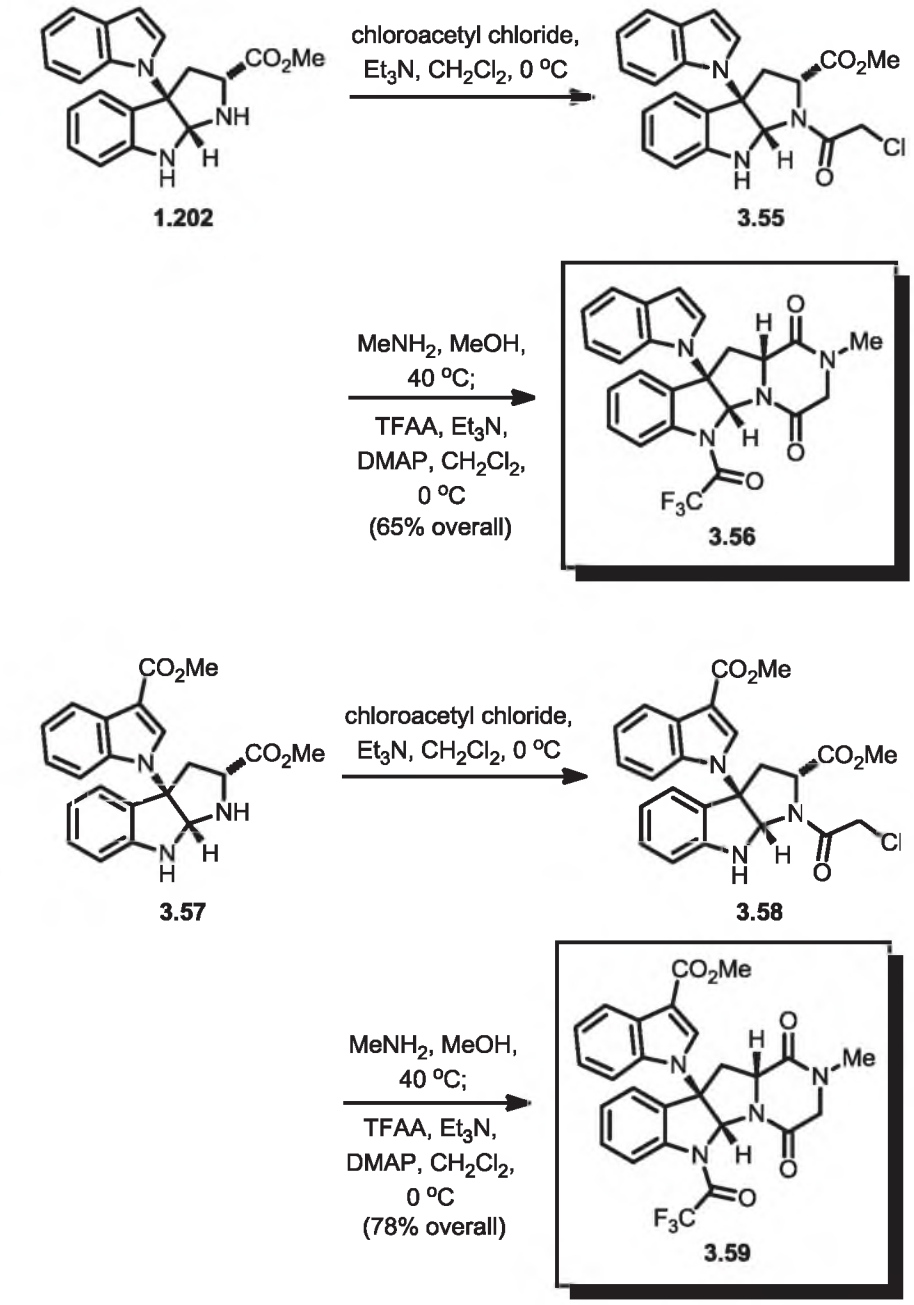
Scheme 3.8. Retrosynthetic Analysis of (−)-Chetomin



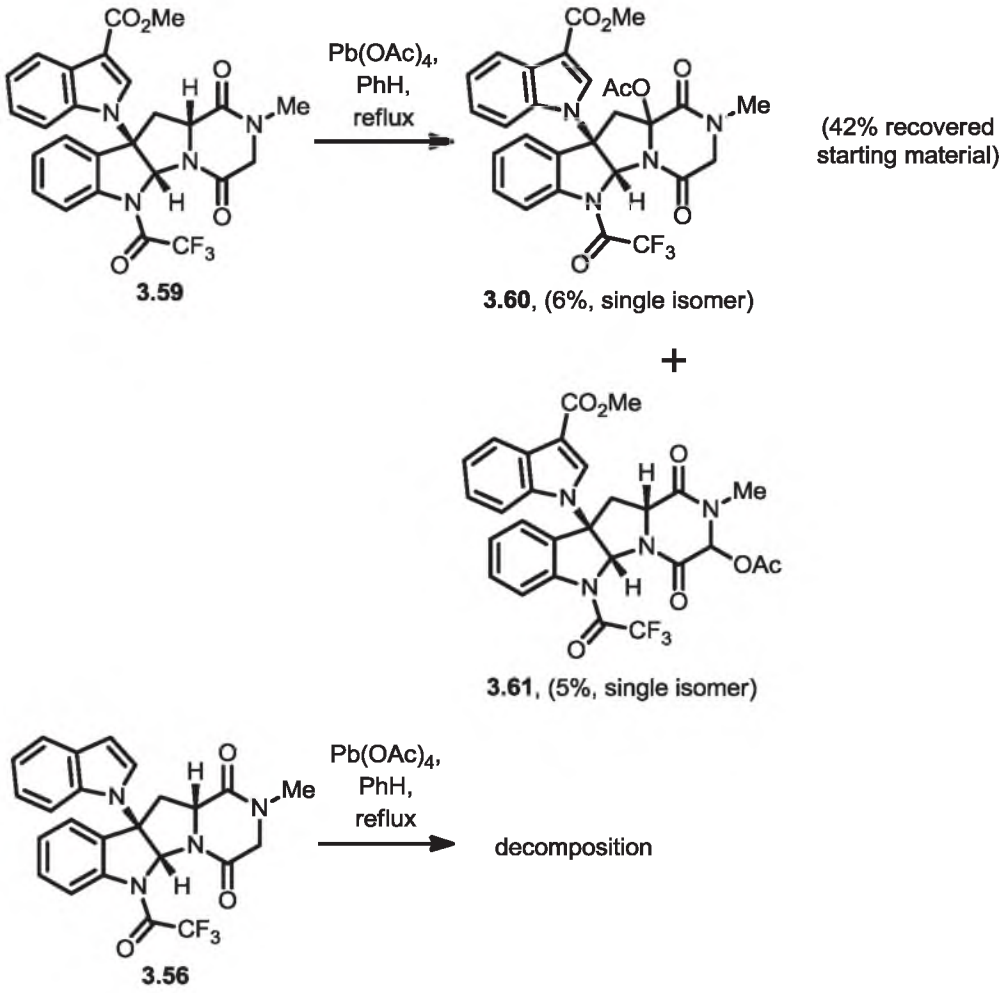
Scheme 3.9. Model Study Design

(Scheme 3.10). Synthesis of model compound **3.56** began with the acylation of known heterodimer **1.202** to provide chloroacetamide **3.55**. Addition of methyl amine and in situ ring closure gives the diketopiperazine **3.56**. Synthesis of model compound **3.59** proceeds in an identical fashion.

When C(3)-ester substituted indole **3.59** was subjected to $Pb(OAc)_4$ in refluxing benzene, miniscule yields of mono-acetoxy compounds **3.60** and **3.61** were obtained as single isomers with the majority of the mass balance being recovered starting material, however di-acetoxy material was not detected.[6] Unsurprisingly, when C(3)-unsubstituted indole **3.56** was subjected to the same conditions, only decomposition was noted presumably through oxidation of the sensitive indole-[2,3]-π double bond (Scheme 3.11).[7] In light of this result, heterodimer **3.56** was not pursued as a viable substrate for oxidation and it was deemed worthwhile to have an electron-withdrawing group at the C(3)-position of indole to prevent excessive oxidation.



Scheme 3.10. Synthesis of Model Heterodimers **3.56** and **3.59**



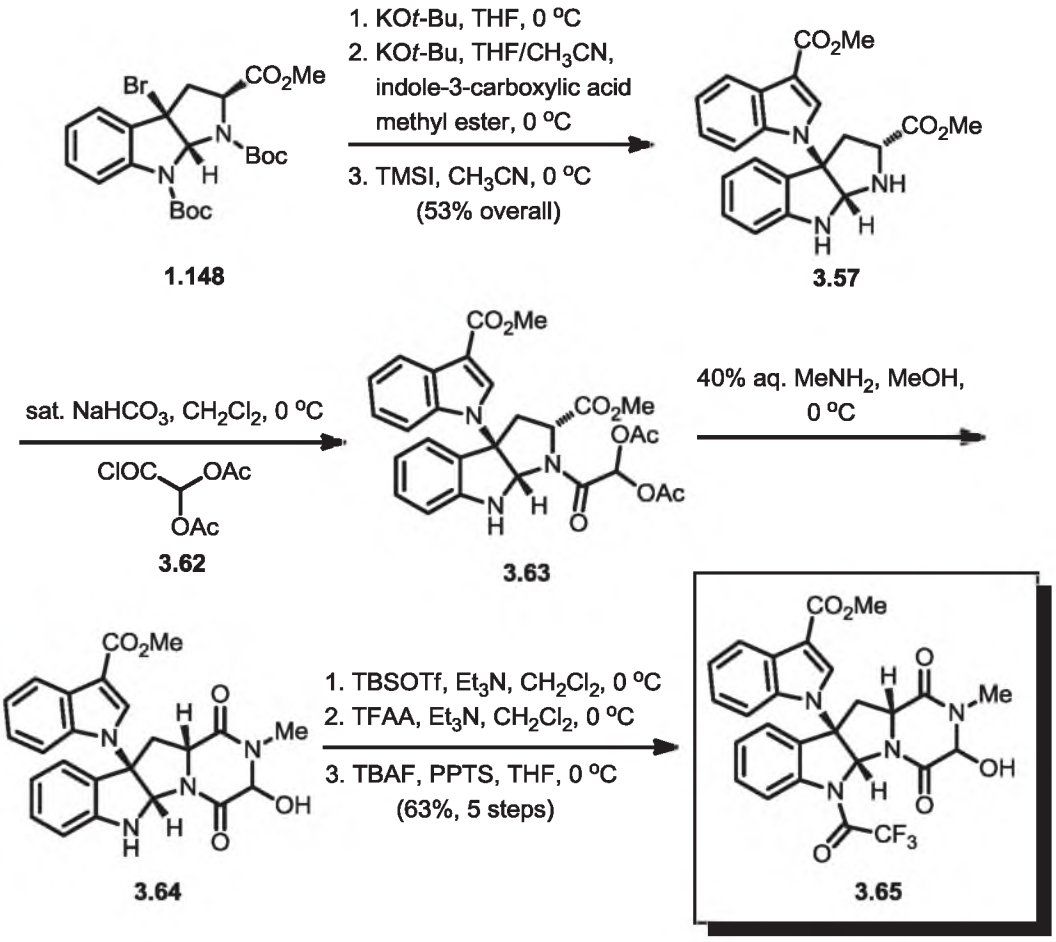
Scheme 3.11. Oxidation Results of Heterodimers **3.56** and **3.59**

Given these successful yet synthetically nonviable results, a second model substrate was examined in the hopes that it would be converted into the appropriately oxidized material more efficiently. Thus, bromopyrroloindoline **1.148** was converted to the cyclopropylazetoindoline, allowed to react with indole-3-carboxylic acid methyl ester, and after Boc group removal gave bisamine **3.57** (Scheme 3.12).[8] Reaction of the bisamine with acyl chloride **3.62** and cyclization using methylamine gave the hydroxylated diketopiperazine **3.64**. After a protection and deprotection sequence the

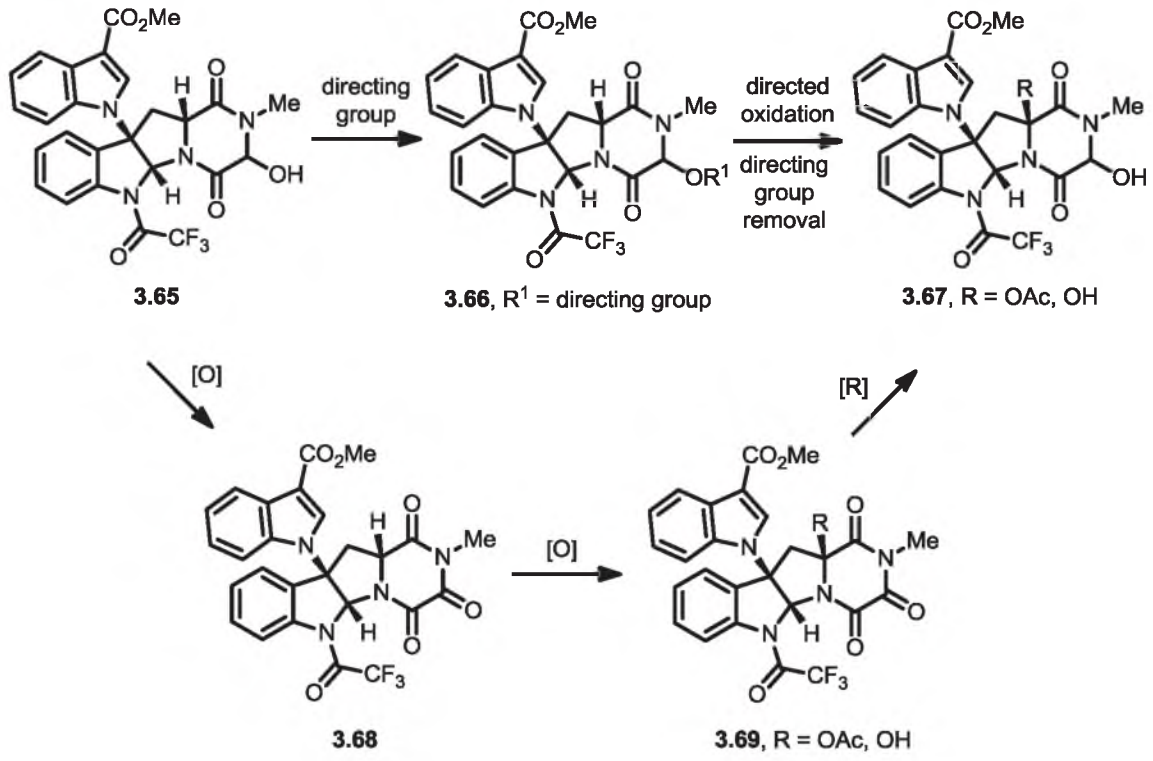
desired substrate **3.65** was obtained. This substrate was designed to contain a hydroxyl group at the alpha position whereas in substrate **3.59** there resides a methylene group. It was envisioned that this compound could be used to either direct oxidation to the other methine position or be iteratively oxidized and then reduced to give an identical product (Scheme 3.13).

In the event, **3.65** was reacted with $Pb(OAc)_4$ in refluxing benzene to yield trioxopiperazine **3.70** directly as an isomeric mixture along with acetate **3.61** (Scheme 3.14). While the exact mechanism for this oxidation is unclear, it is believed to proceed in the fashion shown in either Scheme 3.14 or Scheme 3.15.[9] Ligand exchange with lead tetraacetate affords **3.71** which undergoes homolytic scission to form hydroxy radical **3.72** (Scheme 3.14). Hydrogen abstraction by an acetate radical can produce trioxopiperazine **3.73**. Another ligand exchange with lead tetraacetate gives **3.74**, followed by homolytic scission and trapping the carbon centered radical with an acetate radical affords **3.70**. Alternatively, a 1,5-hydrogen abstraction involving hydroxy radical **3.72** is possible if the hydroxy radical has the desired stereochemistry shown in **3.76** (Scheme 3.15). Trapping the generated carbon centered radical in **3.77** gives **3.78** and then oxidation of the aminal follows that shown in Scheme 3.14.

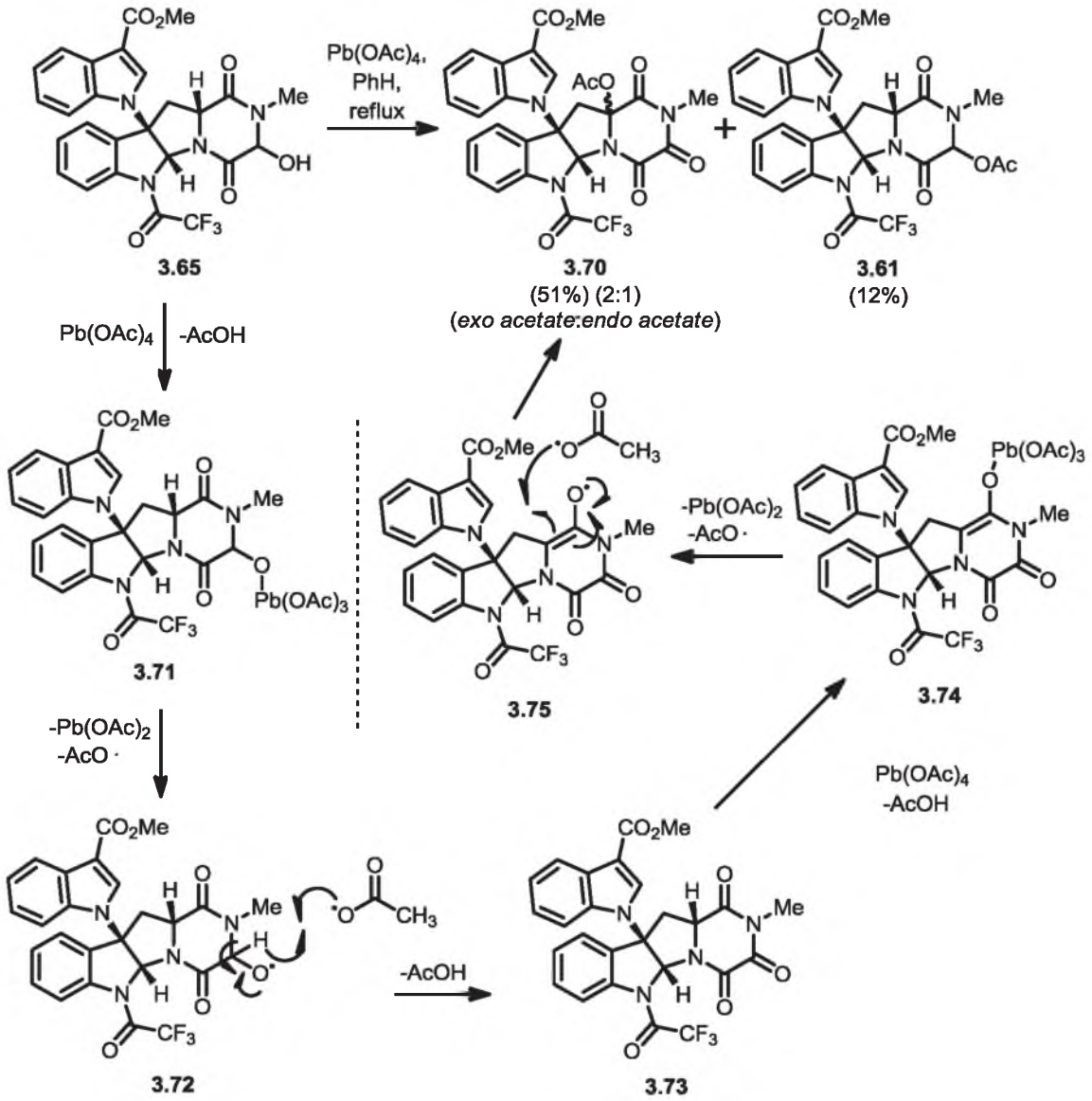
Synthesis of trioxopiperazine **3.70** is fortuitous because the Overman group has shown the possibility of the selective addition of Grignard reagents to one of the carbonyls of a related trioxopiperazine (**3.47**) (Scheme 3.7). Thus, we examined the addition of MeMgBr to the trioxopiperazine **3.70**-*exo* (Scheme 3.16).



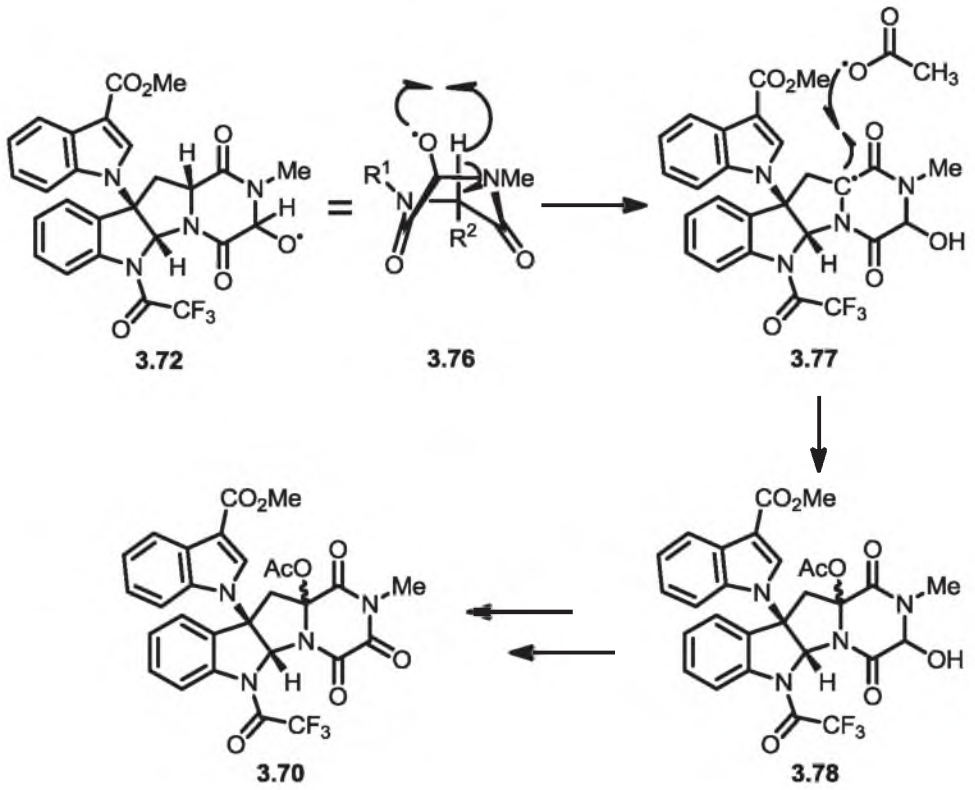
Scheme 3.12. Synthesis of Heterodimer **3.65**



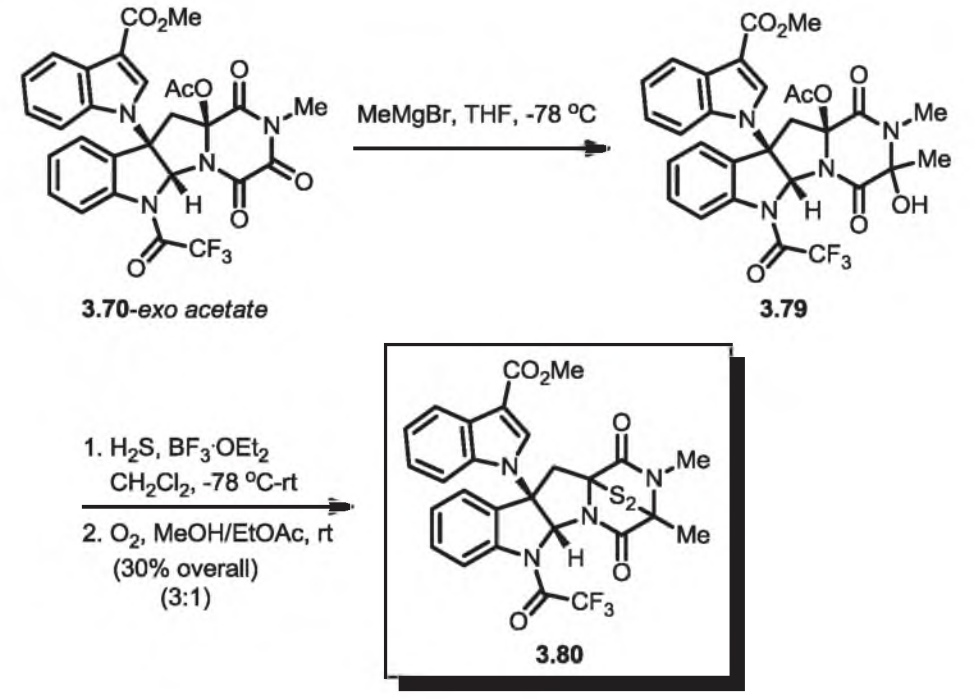
Scheme 3.13. Proposed Oxidation Routes of Heterodimer **3.65**



Scheme 3.14. Oxidation of Heterodimer **3.65** and Mechanistic Rationale



Scheme 3.15. Alternative Mechanism Involving 1,5-Hydrogen Abstraction



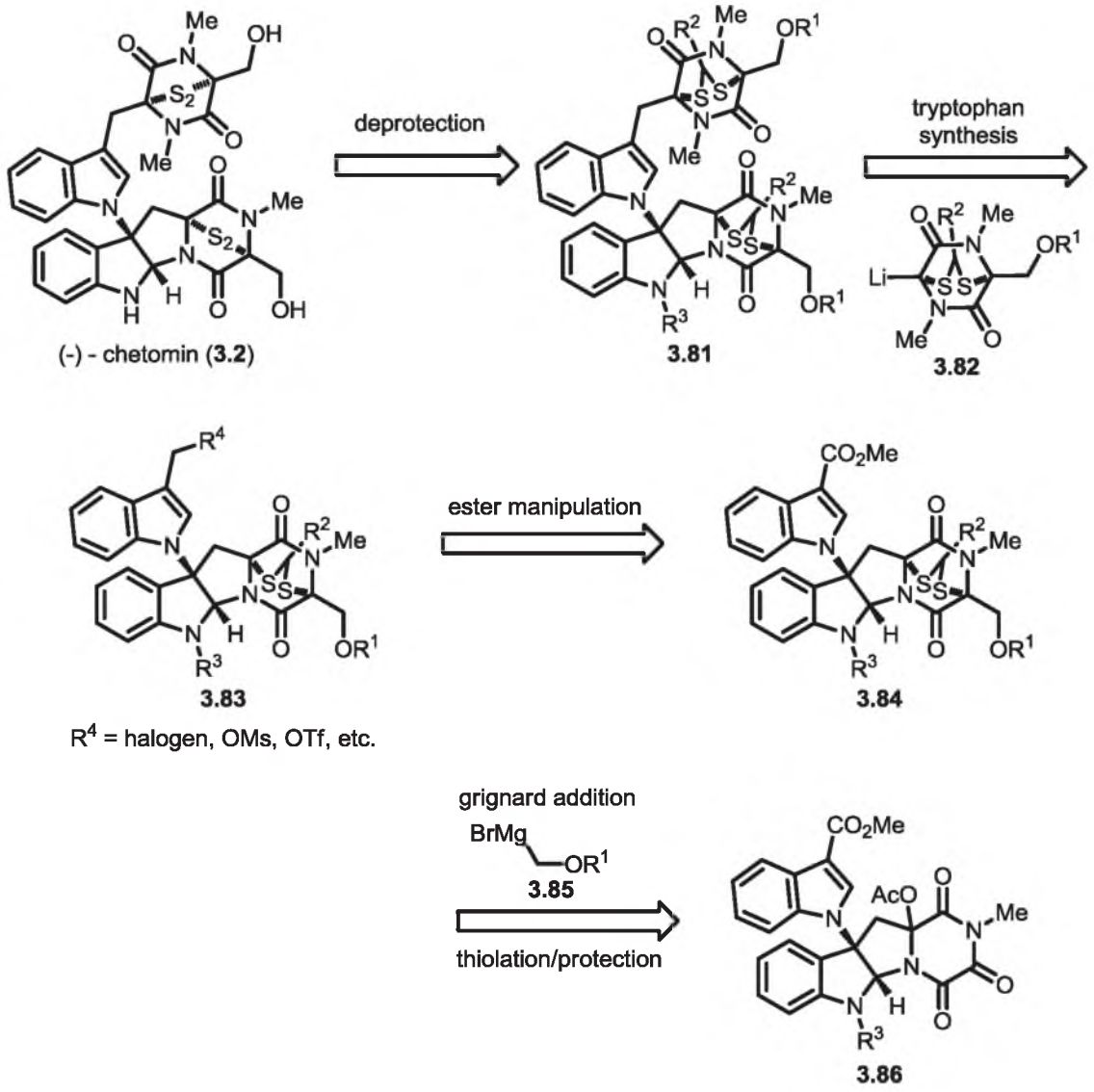
Scheme 3.16. Grignard Addition to **3.70** and Disulfide Synthesis

Fortunately, the Grignard addition to trioxopiperazine **3.70**-*exo acetate* was very efficient and we did not observe byproducts relating to the addition of MeMgBr to the ester or trifluoroacetamide groups. Due to the perceived instability of **3.79**, we immediately converted it to the dithiol followed by oxidation to the epidithiodiketopiperazine **3.80** using Overman's protocol (Scheme 3.16).

Given this promising result, in addition to the ease with which **3.65** could be prepared on a large scale with few chromatography events, we were led to revise our retrosynthetic plan (Scheme 3.17). The plan involves synthesis of chetomin from the deprotection of bis-dithiane **3.81** using the Kishi protocol. The bis-dithiane **3.81** could be synthesized from ester **3.84** by converting the ester to a good leaving group and alkylation with dithiane **3.82**. Finally, **3.84** is made by Grignard addition to trioxopiperazine **3.86**, thiolation, and protection of the dithiol as a dithiane.

Conclusions

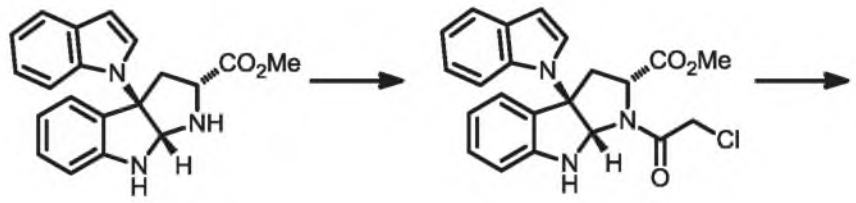
A model study on the synthesis of a C(3)-N(1′) heterodimeric indoline containing an epidithiodiketopiperazine was successfully executed. This involved the development of a novel oxidation protocol for the synthesis of a highly functionalized trioxopiperazine, the successful application of a selective Grignard addition to the trioxopiperazine, and the conversion of the resulting diol to an epidithiodiketopiperazine. Further studies will focus on appending the second epidithiodiketopiperazine required for the total synthesis of chetomin.



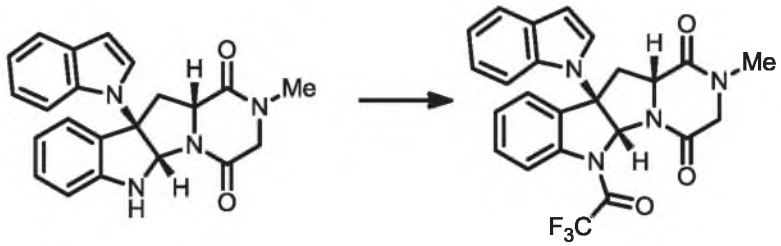
Scheme 3.17. Revised Retrosynthetic Analysis of (−)-Chetomin

Experimental Section

Chemicals were either used as received or purified according to *Purification of Common Laboratory Chemicals*.[10] Glassware was dried in an oven at 130 °C or flame dried and cooled under a dry atmosphere prior to use. All reactions were performed using common dry, inert atmosphere techniques. Reactions were monitored by TLC and visualized by a dual short wave/long wave UV lamp and stained with an ethanolic solution of potassium permanganate or p-anisaldehyde. Column flash chromatography was performed using 230-400 mesh silica gel. NMR spectra were recorded on Varian Unity-300, Varian VXR-500, or Varian Inova-500 spectrometers. Chemical shifts for ^{1}H NMR were reported as δ, parts per million, relative to the signal of tetramethylsilane at 0 ppm. Chemical shifts for ^{13}C NMR were reported as δ, parts per million, relative to the center line signal of the $CDCl_3$ triplet at 77 ppm. Proton and carbon assignments were established using spectral data of similar compounds, ^{1}H nOe analysis, and ^{13}C DEPT NMR. The abbreviations s, bs, d, dd, bd, ddd, t, q, bq, and m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, and multiplet, respectively. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Optical rotations were obtained on a Perkin Elmer Model 343 polarimeter (Na D line) using a microcell with a 1 decimeter path length. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 double focusing high resolution mass spectrometer. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg).



1.202 **3.55**

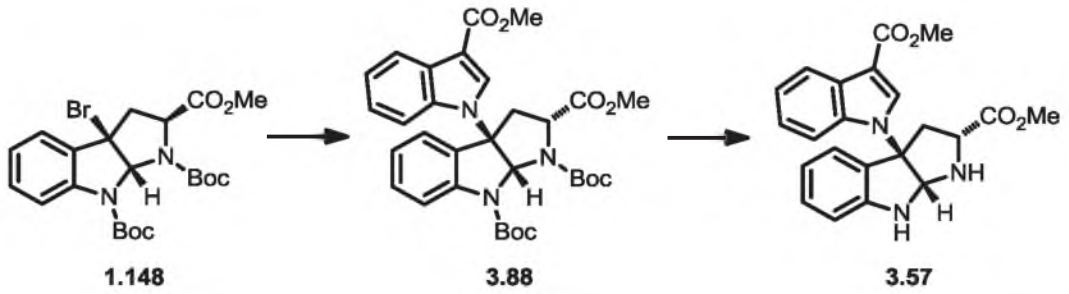


3.87 **3.56**

Preparation of (5a*R*,10b*R*,11a*R*)-10b-(1*H*-indol-1-yl)-2-methyl-6-(2,2,2-trifluoroacetyl)-2,3,5a,6,11,11a-hexahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(10b*H*)-dione (3.56). To a solution of bisamine **1.202** (0.115 g, 0.300 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added Et_3N (0.09 mL, 0.6 mmol) followed by chloroacetyl chloride (0.02 mL, 0.3 mmol). The reaction mixture was quenched with dil. HCl (10 mL) after completion (TLC) and diluted with CH_2Cl_2 (30 mL). The organic layer was washed with H_2O (10 mL), sat. $NaHCO_3$ (10 mL), brine (10 mL), and dried (Na_2SO_4). After concentration, the residue was dissolved in THF/MeOH (3 mL/3 mL) and cooled to 0 °C whereupon methylamine (1.2 mL, 15 mmol, 40 wt.% in H_2O) was added. The reaction was allowed to warm to room temperature over 1 h and stirred until completion (TLC). The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with H_2O (10 mL), brine (10 mL), and dried (Na_2SO_4). After concentration, flash chromatography (50% EtOAc:hexanes-33% acetone:CH_2Cl_2) afforded 0.073 g (65% overall) of **3.87** an beige solid. The diketopiperazine **3.87** (0.082 g, 0.22 mmol) was then dissolved in

CH_2Cl_2 (3 mL) and cooled to 0 °C whereupon DMAP (0.027 g, 0.22 mmol), Et_3N (0.15 mL, 1.1 mmol), and TFAA (0.09 mL, 0.7 mmol) were added sequentially. The reaction was complete immediately and was diluted with CH_2Cl_2 (30 mL) and washed with dil. HCl (10 mL), sat. $NaHCO_3$ (10 mL), brine (10 mL), and dried (Na_2SO_4). Concentration afforded **3.56** in quantitative yield. **3.87**: R_f 0.22 (80% EtOAc:hexanes); $[\alpha]_D = -186.5°$ (c = 0.196, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 3.4 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 7.08 (t, J = 7.3 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 7.3 Hz, 1H), 6.78-6.72 (m, 3H), 6.59 (d, J = 3.4 Hz, 1H), 6.10 (d, J = 3.9 Hz, 1H), 5.47 (d, J = 3.4 Hz, 1H), 4.68 (dd, J = 10.8, 6.4 Hz, 1H), 4.17 (dd, J = 17.1, 1.5 Hz, 1H), 3.83 (d, J = 17.1 Hz, 1H), 3.69 (dd, J = 14.7, 6.3 Hz, 1H), 3.00 (s, 3H), 2.78 (dd, J = 14.7, 11.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 164.2, 146.7, 135.1, 130.3, 130.3, 128.2, 124.2, 123.5, 122.0, 121.4, 120.3, 120.1, 112.0, 110.3, 102.7, 82.3, 73.7, 57.6, 53.6, 40.1, 33.7; IR (neat) 3338, 3051, 2926, 1668, 1611, 1455, 1402, 1346, 1321, 1261, 1215, 1178, 1081, 961 cm^{-1}; LRMS (ESI) calcd for $C_{22}H_{20}N_4O_2Na$ *m/z* ($M+Na^+$) 395.2, found 395.1. **3.56**: R_f 0.34 (80% EtOAc:hexanes); $[\alpha]_D = +260.8°$ (c = 1.288, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.52 (dt, J = 7.7, 1.4 Hz, 1H), 7.44-7.36 (m, 2H), 7.30-7.17(m, 2H), 6.74 (s, 1H), 6.55 (d, J = 3.4 Hz, 1H), 6.40 (dd, J = 3.4, 0.7 Hz, 1H), 4.75 (dd, J = 7.0, 7.0 Hz, 1H), 4.16 (d, J = 16.7 Hz, 1H), 3.70-3.59 (m, 3H), 2.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 164.8, 156.6, 140.5, 133.9, 131.6, 130.8, 130.3, 126.9, 126.6, 126.5, 122.3, 120.6, 119.1, 117.6, 110.2, 102.6, 78.9 (q, J = 5.0 Hz), 71.4, 57.2, 53.6, 33.9, 33.0; IR (neat) 2951, 1757, 1694, 1601, 1540, 1484, 1436, 1399, 1381, 1354, 1312, 1255, 1203, 1150, 1110, 1060, 1009, 946, 884, 736 cm^{-1}; LRMS (ESI) calcd for $C_{24}H_{20}F_3N_4O_3$ *m/z* ($M+H^+$) 469.1,

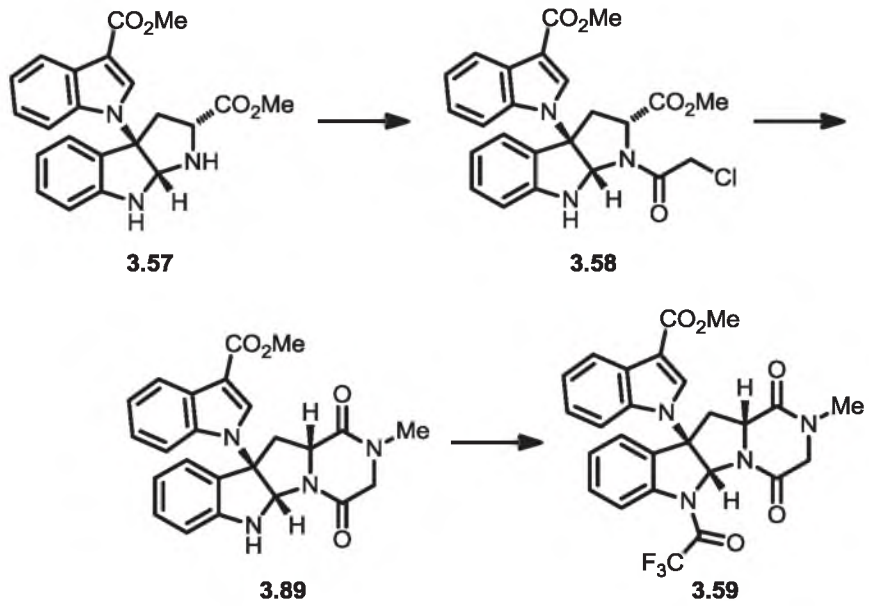
found 469.2.



Preparation of (2*R*,3a*R*,8a*R*)-1,8-di-*tert*-butyl 2-methyl 3a-(3-(methoxycarbonyl)-1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (3.97) and (2*R*,3a*R*,8a*R*)-methyl 3a-(3-(methoxycarbonyl)-1*H*-indol-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3.57). To a solution of bromopyrroloindoline **1.148** (1.514 g, 3.045 mmol) in THF (24 mL) at 0 °C was added dropwise KO*t*Bu (4.0 mL, 1M solution in THF, 4.0 mmol) over 30 min. via syringe pump in duplicate. The reaction mixtures were quenched with sat $NaHCO_3$ (2 ml each), combined, and the volatiles removed under reduced pressure no more than 40 °C. The residue was diluted with CH_2Cl_2 (120 mL), washed with brine (20 mL), dried (sat. Na_2SO_4), and concentrated. The residue was dissolved in THF (12 mL) and added at once to a solution of methyl indole-3-carboxylate (1.840 g, 10.50 mmol) and KO*t*Bu (7.2 mL, 1M solution in THF, 7.2 mmol) in THF:CH_3CN (1:1, 24 mL) at 0 °C and stirred for 5 min. before being quenched by sat. $NaHCO_3$ (2 ml) and the volatiles removed under reduced pressure to provide crude adduct **3.88** (an analytical sample was obtained by flash chromatography (20% EtOAc:hexanes)). The residue was dissolved in CH_2Cl_2 (120 mL), washed with brine (20 mL), dried (Na_2SO_4), and concentrated. To this mixture in

CH_3CN (24 mL) at 0 °C was added TMSI (5.7 mL, 41 mmol) and the mixture was stirred for 1.0 h at 0 °C. The reaction mixture was then quenched with sat. $NaHCO_3$ (40 mL) and the volatiles removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (120 mL) and washed with sat. $NaHCO_3$ (60 mL), brine (20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (50-100% EtOAc:hexanes) afforded 1.250 g (53% from **1.148**) of bis-amine **3.57** as an oil. **3.88**: foam; R_f 0.33 (33% EtOAc:hexanes); $[\alpha]_D$ = +37.5 (*c* = 0.722, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23-8.20 (m, 1H), 7.69 (s, 1H), 7.68 (bs, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.35-7.26 (m, 4H), 7.13 (t, *J* = 7.3 Hz, 1H), 6.84 (s, 1H), 4.93 (bs, 1H), 3.84 (s, 3H), 3.54 (dd, *J* = 13.2, 9.3 Hz, 1H), 3.23 (s, 3H), 3.03 (d, *J* = 13.2 Hz, 1H), 1.53 (s, 9H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 164.9, 152.9, 151.6, 143.6, 134.8, 132.7, 131.3, 128.1, 127.8, 125.4, 123.6, 123.6, 123.2, 122.2, 118.0, 111.7, 107.5, 82.2, 81.5, 79.5, 72.9, 59.2, 52.0, 50.8, 38.3, 28.1, 28.0; IR (neat) 2979, 2951, 1757, 1710, 1604, 1538, 1482, 1456, 1393, 1368, 1337, 1268, 1211, 1159, 1098, 928, 856 cm^{-1}; LRMS (ESI) calcd for $C_{32}H_{37}N_3O_8Na$ *m/z* ($M+Na^+$) 614.3, found 614.2. **3.57**: foam; R_f 0.15 (50% EtOAc:hexanes); $[\alpha]_D$ = −38.2 (*c* = 0.206, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.3 Hz, 1H), 7.95 (s, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.28-7.23 (m, 1H), 7.23-7.18 (m, 2H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.82 (t, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 5.57 (s, 1H), 4.58 (s, 1H), 4.24 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.88 (s, 3H), 3.48 (dd, *J* = 13.2, 7.8 Hz, 1H), 3.35 (s, 3H), 3.00 (dd, *J* = 13.2, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 165.4, 149.9, 135.4, 132.8, 131.0, 128.1, 126.3, 125.6, 122.8, 122.1, 122.0, 119.8, 112.5, 111.0, 107.1, 81.6, 76.4, 60.3, 52.1, 51.1, 40.6; IR (neat) 3360, 3053, 2949, 1733, 1698, 1608, 1536, 1485, 1459, 1436, 1380, 1322, 1265, 1215, 1168, 1119, 1100, 1036, 1020, 931, 747 cm^{-1}; LRMS (ESI) calcd for

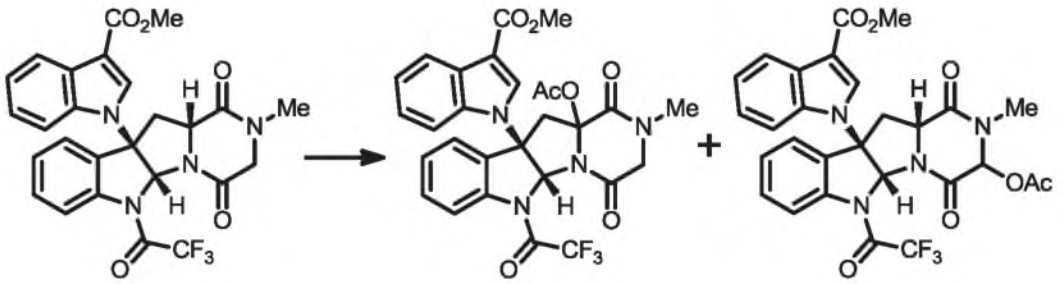
$C_{22}H_{21}N_3O_4Na$ *m/z* ($M+Na^+$) 414.2, found 414.1.



Preparation of methyl 1-((5a*R*,10b*R*,11a*R*)-2-methyl-1,4-dioxo-6-(2,2,2-trifluoroacetyl)-2,3,4,5a,6,10b,11,11a-octahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indol-10b-yl)-1*H*-indole-3-carboxylate (3.59). To a solution of bisamine **3.57** (0.395 g, 1.01 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.28 mL, 2.0 mmol) followed by chloroacetyl chloride (0.084 mL, 1.1 mmol). The reaction was quenched with dil. HCl (20 mL) after completion (TLC) and diluted with CH_2Cl_2 (60 mL). The organic layer was washed with H_2O (20 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL), and dried (Na_2SO_4). After concentration, the residue was dissolved in THF/MeOH (6 mL/6 mL) and cooled to 0 °C whereupon methylamine (1.9 mL, 25 mmol, 40 wt.% in H_2O) was added. The reaction was allowed to warm to room temperature over 1 h and stirred until completion (TLC). The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and washed with H_2O (20 mL), brine (20 mL), and dried (Na_2SO_4). After concentration, flash

chromatography (50% EtOAc:hexanes-33% acetone:CH_2Cl_2) afforded 0.337 g (78% overall) of **3.89** an beige solid. The diketopiperazine **3.89** (0.293 g, 0.681 mmol) was then dissolved in CH_2Cl_2 (6 mL) and cooled to 0 °C whereupon DMAP (0.083 g, 0.68 mmol), Et_3N (0.47 mL, 3.4 mmol), and TFAA (0.29 mL, 2.0 mmol) were added sequentially. The reaction was complete immediately and was diluted with CH_2Cl_2 (30 mL) and washed with dil. HCl (10 mL), sat. $NaHCO_3$ (10 mL), brine (10 mL), and dried (Na_2SO_4). Concentration afforded **3.59** in quantitative yield. **3.89**: R_f 0.15 (80% EtOAc:hexanes); $[\alpha]_D = -178.2°$ (*c* = 1.010, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.82-6.70 (m, 3H), 6.11 (d, *J* = 3.6 Hz, 1H), 5.78 (d, *J* = 3.7 Hz, 1H), 4.54 (dd, *J* = 11.5, 5.9 Hz, 1H), 4.16 (d, *J* = 17.3 Hz, 1H), 3.93 (s, 3H), 3.81 (d, *J* = 17.0 Hz, 1H), 3.71 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.97 (s, 3H), 2.76 (dd, *J* = 15.0, 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 165.1, 164.2, 146.9, 135.5, 131.0, 130.6, 127.9, 127.1, 123.2, 123.1, 122.4, 122.0, 120.1, 112.4, 110.4, 108.1, 82.0, 74.3, 57.2, 53.4, 51.2, 39.9, 33.7; IR (neat) 3336, 3122, 3054, 2948, 1670, 1611, 1536, 1484, 1457, 1440, 1402, 1380, 1320, 1266, 1214, 1119, 1058, 750 cm^{-1}; LRMS (ESI) calcd for $C_{24}H_{23}N_4O_4$ *m/z* ($M+H^+$) 431.2, found 431.2. **3.59**: R_f 0.28 (80% EtOAc:hexanes); $[\alpha]_D = +201.1°$ (*c* = 1.116, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29-8.19 (m, 2H), 7.68 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.57 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.45 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.44-7.32 (m, 3H), 7.25 (s, 1H), 6.78 (s, 1H), 4.76 (dd, *J* = 8.7, 6.3 Hz, 1H), 4.16 (d, *J* = 17.0 Hz, 1H), 3.82 (s, 3H), 3.66 (d, *J* = 17.0 Hz, 1H), 3.61 (dd, *J* = 8.7, 3.3 Hz, 1H), 2.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 165.1, 165.0, 156.8, 140.8, 134.5, 133.2, 132.5, 129.3, 128.7, 127.6, 127.1, 123.9, 123.5, 123.1, 119.6, 110.9,

108.5, 79.1 (q, J = 5.5 Hz), 72.0, 57.6, 53.9, 51.4, 34.2, 33.2; IR (neat) 2951, 1757, 1694, 1601, 1540, 1484, 1436, 1454, 1381, 1354, 1399, 1312, 1255, 1203, 1150, 1110, 1060, 1009 cm^{-1}; LRMS (ESI) calcd for $C_{26}H_{22}F_3N_4O_5$ *m/z* ($M+H^+$) 527.2, found 527.2.

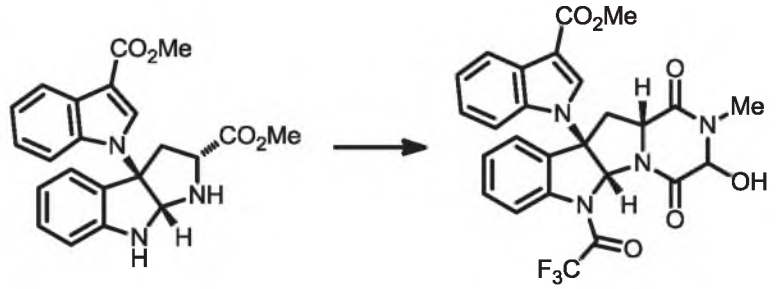


3.59 **3.60** **3.61**

Preparation of methyl 1-((5a*R*,10b*R*,11a*R*)-3-acetoxy-2-methyl-1,4-dioxo-6-(2,2,2-trifluoroacetyl)-2,3,4,5a,6,10b,11,11a-octahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indol-10b-yl)-1*H*-indole-3-carboxylate (3.60) and methyl 1-((5aS,10bR)-11a-acetoxy-2-methyl-1,4-dioxo-6-(2,2,2-trifluoroacetyl)-2,3,4,5a,6,10b,11,11a-octahydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indol-10b-yl)-1H-indole-3-carboxylate (3.61). To a solution of diketopiperazine (**3.59**) (0.024 g, 0.046 mmol) in benzene (2.5 mL) was added lead tetraacetate (0.086 g, 0.18 mmol) at once. The mixture was refluxed for 2 h and then cooled to rt whereupon lead tetraacetate (0.180 g, 0.406 mmol) was added and the mixture brought to reflux for 18 h. The mixture was then cooled to rt, quenched with sat. $NaHCO_3$ (5 mL), diluted with EtOAc (10 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3 x 5 mL), the organic extracts combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Preparatory TLC (50% EtOAc:hexanes) afforded 0.001 g (5%) of **3.61**, 0.002 g (6%) of **3.60**, and 0.010 g (42%) of **3.59**. **3.61**: R_f 0.48 (50% EtOAc:hexanes); $[\alpha]_D$ = +129.1° (*c*

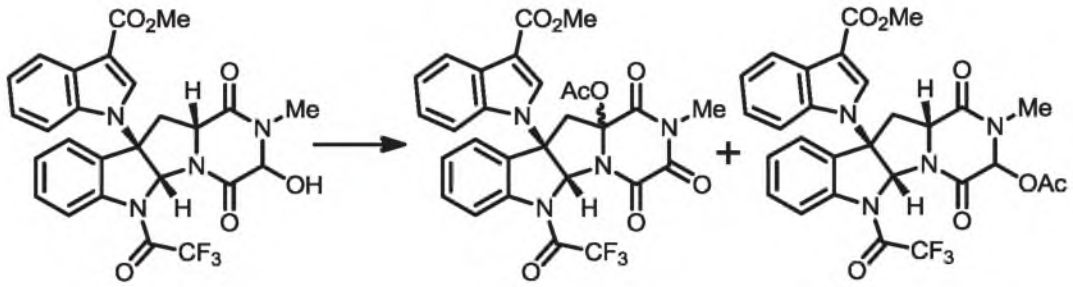
= 0.604, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.29-8.25 (m, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.67 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.61-7.54 (m, 1H), 7.49-7.35 (m, 4H), 7.23 (s, 1H), 6.81 (s, 1H), 5.91 (s, 1H), 4.98 (dd, *J* = 8.9, 6.2 Hz, 1H), 3.82 (s, 3H), 3.67-3.61 (m, 2H), 2.89 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 167.2, 164.6, 161.3, 156.2, 140.4, 134.2, 132.9, 132.3, 128.6, 128.4, 127.3, 126.7, 123.7, 123.2, 122.9, 119.4, 110.6, 108.3, 81.5, 79.0 (q, *J* = 5.0 Hz), 71.7, 56.7, 51.1, 33.6, 32.3, 20.6; IR (neat) 2921, 1751, 1670, 1541, 1484, 1457, 1436, 1395, 1349, 1312, 1257, 1207, 1157, 1043, 1013, 990, 937 cm^{-1}; LRMS (ESI) calcd for $C_{28}H_{28}F_3N_4O_7Na$ *m/z* ($M+Na^+$) 607.2, found 607.1.

3.60: R_f 0.22 (50% EtOAc:hexanes); $[\alpha]_D$ = +71.2° (*c* = 0.098, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.8 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 7.77 (s, 1H), 7.56 (t, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.28-7.24 (m, 1H), 7.23-7.18 (m, 1H), 6.67 (s, 1H), 4.27 (d, *J* = 17.6 Hz, 1H), 3.94 (d, *J* = 15.6 Hz, 1H), 3.88 (s, 3H), 3.74 (d, *J* = 17.6 Hz, 1H), 3.56 (d, *J* = 15.6 Hz, 1H), 2.89 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 165.0, 164.2, 162.1, 140.6, 135.7, 132.9, 132.2, 131.1, 128.3, 127.6, 125.8, 123.9, 123.0, 122.8, 119.1, 114.8, 111.3, 109.2, 89.6, 80.9, 71.4, 53.8, 51.4, 44.8, 34.1, 29.9, 21.3; IR (neat) 2921, 1751, 1670, 1541, 1484, 1457, 1436, 1395, 1349, 1312, 1257, 1207, 1157, 1043, 1013, 990, 937 cm^{-1}; LRMS (ESI) calcd for $C_{28}H_{23}F_3N_4O_7Na$ *m/z* ($M+Na^+$) 607.2, found 607.1.



Preparation of (5a*R*,10b*R*,11a*R*)-3-hydroxy-10b-(1*H*-indol-1-yl)-2-methyl-6-(2,2,2-trifluoroacetyl)-2,3,5a,6,11,11a-hexahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(10b*H*)-dione (3.65). To a solution of bis-amine (**3.57**) (1.200 g, 3.066 mmol) in EtOAc (100 mL) and sat. $NaHCO_3$ (20 mL) at 0 °C was added acid chloride **3.62** (0.656 g, 3.37 mmol) in CH_2Cl_2 (4 mL) slowly dropwise. The mixture was allowed to stir until consumption of the starting material (TLC) and then the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 20 mL), the organic extracts combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was diluted with MeOH (60 mL) and cooled to 0 °C followed by the addition of $MeNH_2$ (12 mL, 40 wt.% in water, 0.15 mol). The mixture was allowed to stir for 15 min. and then was diluted with EtOAc (100 mL) and water (60 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and then the combined organics were washed with brine, dried (Na_2SO_4), and concentrated. The residue was then dissolved in CH_2Cl_2 (60 mL) and cooled to 0 °C followed by addition of Et_3N (0.85 mL, 6.1 mmol) and then TBSOTf (1.1 mL, 4.6 mmol). The mixture was allowed to stir for 5 min. and was then quenched with sat. $NaHCO_3$ (20 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organics were washed with 1M HCl (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was then

dissolved in CH_2Cl_2 (60 mL) and cooled to 0 °C followed by the addition of Et_3N (1.3 mL, 9.2 mmol) and TFAA (0.88 mL, 6.1 mmol). The mixture was allowed to stir until completion (TLC) and then quenched with 1M HCl (20 mL)and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organics were washed with sat. $NaHCO_3$ (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was then dissolved in THF (60 mL) and PPTS (0.912 g, 3.63 mmol) was added followed by TBAF (3.6 mL, 1M in THF, 3.6 mmol) at room temperature. The mixture was then concentrated at 40 °C and diluted with CH_2Cl_2 (100 mL) . The organic layer was washed with 1M HCl (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (50-75% EtOAc:hexanes) afforded 1.059 g (64% over 5 steps) of **3.65** as a foam. **3.65**: R_f 0.13 (50% EtOAc:hexanes); $[\alpha]_D$ = +181.4° (*c* = 1.446, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28-8.21 (m, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.61-7.53 (m, 1H), 7.50-7.30 (m, 4H), 7.23 (s, 1H), 6.77 (s, 1H), 5.43 (s, 1H), 5.06 (dd, *J* = 9.2, 6.3 Hz, 1H), 4.94 (s, 1H), 3.82 (s, 3H), 3.65-3.56 (m, 2H), 2.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 165.2, 165.0, 156.2, 140.3, 134.2, 133.0, 132.3, 129.1, 128.3, 127.5, 126.8 123.8, 123.1, 123.0, 119.2, 117.5, 110.6 108.2, 83.0, 79.2 (q, *J* = 4.5 Hz), 71.7, 56.3, 51.2, 32.8, 32.4; IR (neat) 3391, 2951, 1693, 1602, 1541, 1485, 1454, 1440, 1402, 1383, 1354, 1313, 1257, 1211, 1152, 1112, 1042, 962, 738 cm^{-1}; LRMS (ESI) calcd for $C_{26}H_{21}F_3N_4O_6Na$ *m/z* ($M+Na^+$) 565.1, found 565.1.

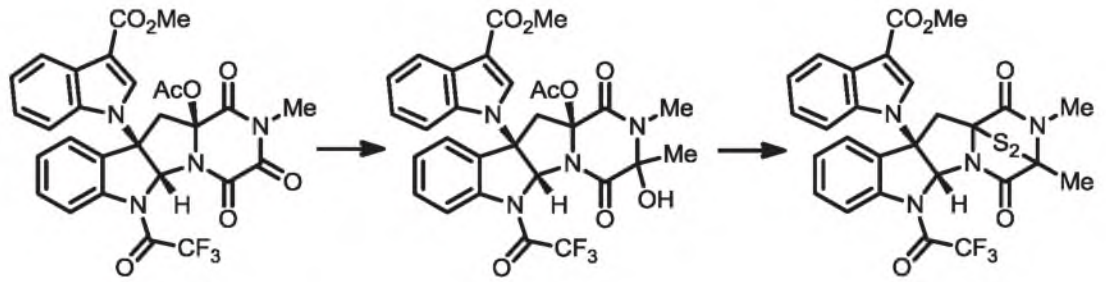


3.65 **3.70** **3.61**

(2:1) (*exo acetate*:*endo acetate*)

Preparation of methyl 1-((5a*S*,10b*R*)-11a-acetoxy-2-methyl-1,3,4-trioxo-6-(2,2,2-trifluoroacetyl)-2,3,4,5a,6,10b,11,11a-octahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indol-10b-yl)-1*H*-indole-3-carboxylate (3.70) and methyl 1-((5a*R*,10b*R*,11a*R*)-3-acetoxy-2-methyl-1,4-dioxo-6-(2,2,2-trifluoroacetyl)-2,3,4,5a,6,10b,11,11a-octahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indol-10b-yl)-1*H*-indole-3-carboxylate (3.61). To a solution of **3.65** (0.336 g, 0.618 mmol) in benzene (24 mL) was added $Pb(OAc)_4$ (2.307 g, 4.942 mmol) at rt under N_2. The mixture was immediately brought to reflux for 1.0 h followed by cooling to rt and was then diluted with EtOAc (100 mL) and quenched carefully with sat. $NaHCO_3$ (100 mL) and separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine (40 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (33-50% EtOAc:hexanes) afforded 0.182 g (51%) of **3.70** (an analytical sample of **3.70**-*endo acetate* and **3.70**-*exo acetate* were obtained by flash chromatography (25% EtOAc:hexanes)) and 0.043 g (12%) of **3.61** as foams. **3.70**-*endo acetate*: R_f 0.61 (50% EtOAc:hexanes); $[\alpha]_D = -109.1°$ (*c* = 0.318, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.3 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.89 (s, 1H), 7.59-7.54 (m, 1H), 7.48-7.38 (m, 3H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.23-7.19 (m, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 3.86 (s, 3H), 3.84 (d, *J* = 14.2 Hz, 1H), 3.45 (d, *J* = 13.7, 1H), 3.24 (s, 3H), 1.54 (s, 3H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 169.7, 164.9, 163.6, 155.6, 152.5, 140.8, 135.0, 132.0, 131.7, 130.6, 128.0, 127.5, 125.5, 124.3, 123.1, 122.9, 118.2, 110.4, 109.1, 89.1, 80.2 (q, J = 3.8 Hz), 71.4, 51.4, 47.0, 27.7, 20.1; IR (neat) 3057, 2953, 1739, 1697, 1609, 1542, 1484, 1456, 1437, 1408, 1350, 1321, 1272, 1211, 1158, 1095, 1052, 1012, 929, 888, 853, 767, 740 cm^{-1}; LRMS (ESI) calcd for $C_{28}H_{21}F_3N_4O_8Na$ ($M+Na^+$) *m/z* 621.1, found 621.1. **3.70**-*exo acetate*: R_f 0.55 (50% EtOAc:hexanes); $[\alpha]_D$ = +80.4° (*c* = 0.310, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 7.8 Hz, 2H), 7.67 (s, 1H), 7.61 (t, J = 7.3 Hz, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.33 (t, J = 7.1 Hz, 1H), 7.29-7.21 (m, 2H), 6.67 (s, 1H), 4.05 (d, J = 15.6 Hz, 1H), 3.88 (s, 3H), 3.48 (d, J = 16.1 Hz, 1H), 3.20 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 164.6, 163.8, 155.1, 150.9, 135.3, 132.6, 132.5, 128.2, 127.8, 125.5, 123.9, 123.1, 122.9, 119.4, 116.7, 114.4, 110.7, 109.4, 88.6, 80.5 (q, J = 4.6 Hz), 51.3, 45.2, 27.8, 21.0; IR (neat) 2952, 1754, 1695, 1601, 1541, 1484, 1457, 1437, 1367, 1343, 1311, 1259, 1204, 1149, 1117, 1097, 1040, 1008, 986, 922, 877, 861, 731 cm^{-1}; LRMS (ESI) calcd for $C_{28}H_{21}F_3N_4O_8Na$ ($M+Na^+$) *m/z* 621.1, found 621.1.



Preparation of methyl 1-((3*R*,5a*S*,10b*R*,11a*R*)-2,3-dimethyl-1,4-dioxo-6-(2,2,2-trifluoroacetyl)-1,2,3,4,5a,6,10b,11-octahydro-3,11a-

epidithiopyrazino[1',2':1,5]pyrrolo[2,3-*b*]indol-10b-yl)-1*H*-indole-3-carboxylate (3.80). To a solution of **3.70**-*exo acetate* (0.093 g, 0.16 mmol) in THF (4 mL) at −78 °C was added MeMgBr (0.10 mL, 0.31 mmol, 3.0 M solution in Et_2O) slowly dropwise. The reaction mixture was immediately quenched with AcOH (0.5 mL) and diluted with EtOAc (30 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organics washed with sat. $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in CH_2Cl_2 (3 mL) and cooled to −78 °C whereupon H_2S gas was bubbled through the solution. Immediately after introduction of the gas, $BF_3{\cdot}OEt_2$ (0.2 mL, 1.6 mmol) was added dropwise and the H_2S gas allowed to bubble through for 15 min. at −78 °C. The solution was warmed rt over 30 min. while continuing to bubble H_2S gas through the reaction mixture. After 2 h, the H_2S gas balloon was replaced with a nitrogen balloon and the reaction mixture purged of H_2S gas for 30 min. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with sat. $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in MeOH:EtOAc (3 mL, 2:1) and O_2 gas was bubbled through the solution for 30 min. whereupon the flask was sealed and left to stir overnight. Concentration and flash chromatography (33%-50% EtOAc:hexanes) afforded 0.022 g (30% overall) of disulfide **3.80** as a foam as a 3:1 mixture of diastereomers. **3.80**: R_f = 0.27 (33% EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30-8.24 (m, 1H), 8.18 (bs, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.58-7.50 (m, 2H), 7.40-7.32 (m, 2H), 7.28-7.22 (m, 1H), 7.11 (s, 1H), 4.55 (d, *J* = 15.6 Hz, 1H), 3.86 (s, 3H), 3.10 (s, 3H), 3.01 (d, *J* = 15.6 Hz, 1H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (selected peaks) 164.8, 164.7, 134.4, 132.6, 132.0, 128.4, 128.1, 127.6, 127.5, 126.0, 125.6, 124.3, 124.2, 123.2, 123.1, 122.4, 119.8,

119.5, 116.8, 114.5, 110.7, 108.8, 78.9, 73.2, 71.7, 51.2, 40.1, 27.7, 18.1; HRMS (ESI) calcd for $C_{27}H_{21}F_3N_4O_5S_2Na$ *m/z* ($M+Na^+$): 625.0803, found 625.0817.

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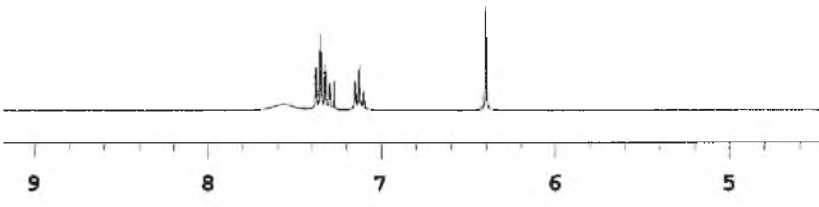
APPENDIX A

NMR SPECTRA CHAPTER 1


9
8
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6
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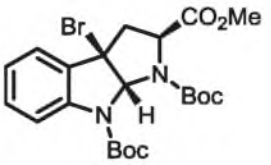
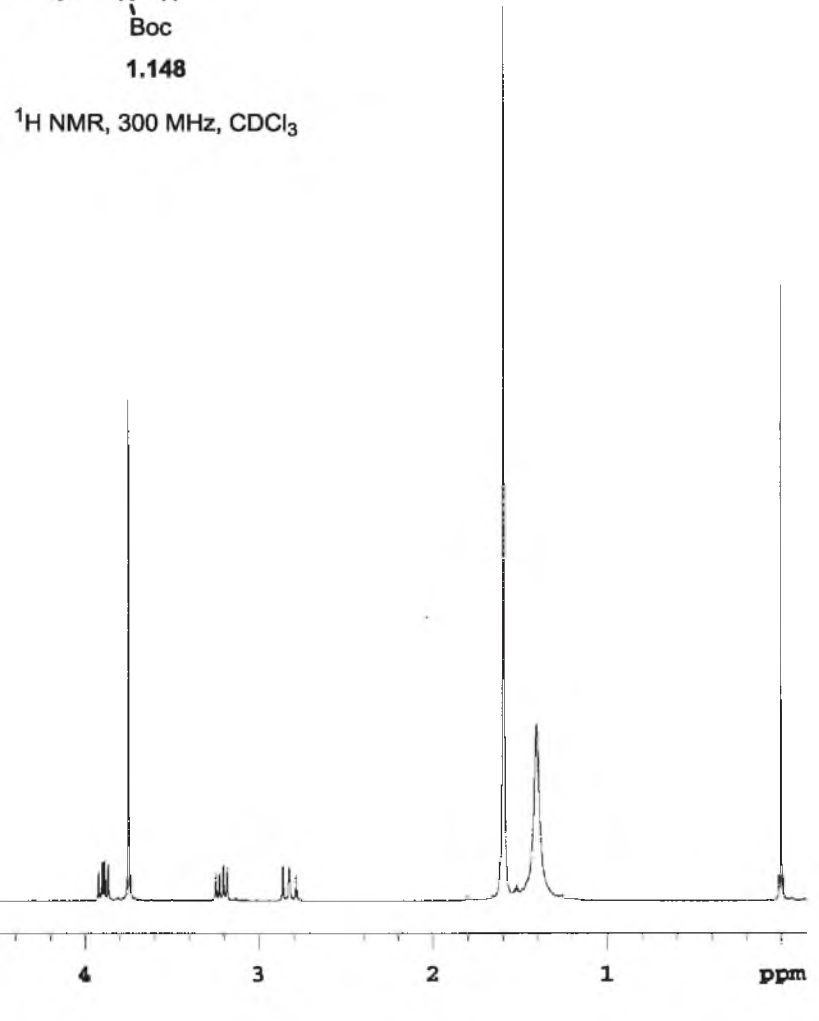
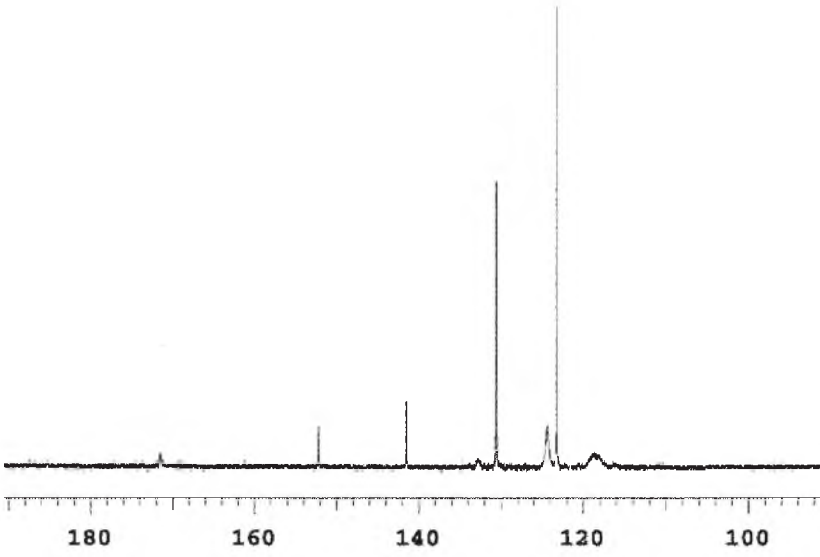
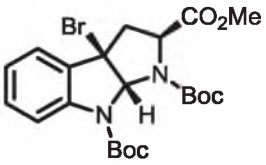


1.148

^{1}H NMR, 300 MHz, $CDCl_3$

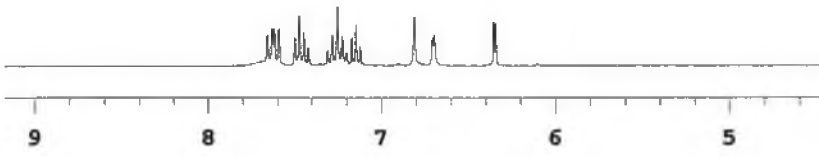



180
160
140
120
100



1.148

^{13}C NMR, 125 MHz, $CDCl_3$


9
8
7
6
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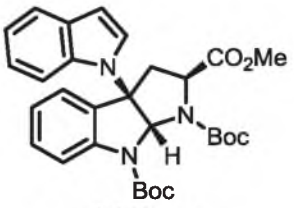
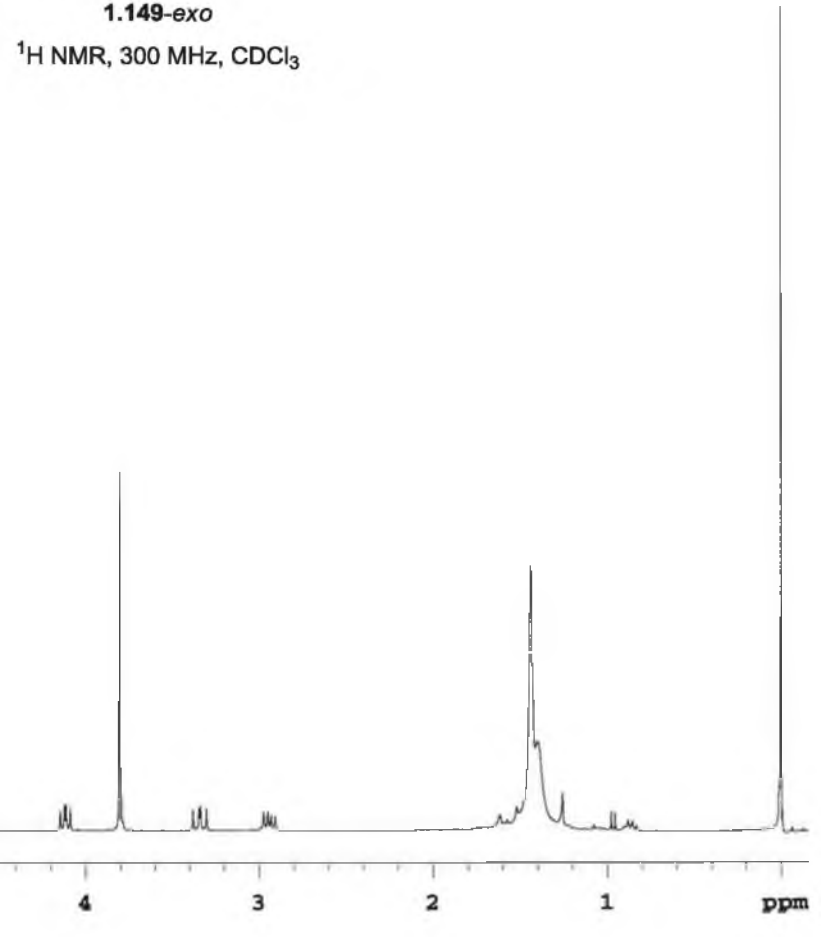


1.149-*exo*

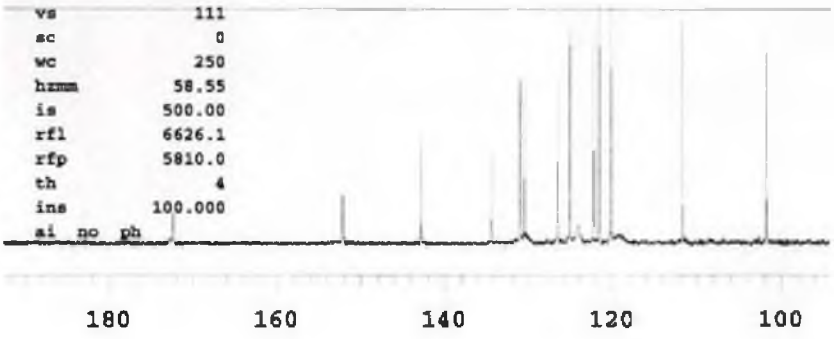
^{1}H NMR, 300 MHz, $CDCl_3$

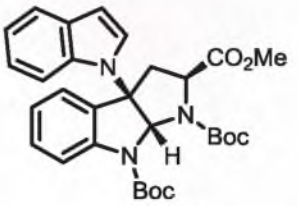


13C OBSERVE

exp2 std13c 102a

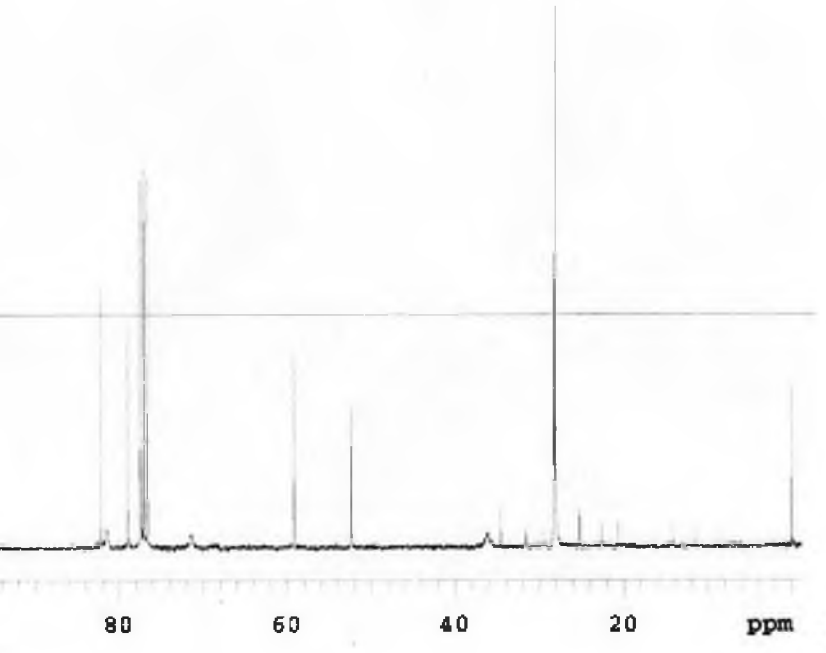
SAMPLE		DEC. & VT	
date	May 10 2008	dfrq	300.078
solvent	CDCl3	dn	H1
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	75.462	dm	yyy
tn	C13	dmm	w
at	3.878	dmf	11200
np	128000	dseq	
sw	16501.7	dres	1.0
fb	9200	homo	n
bs	4	PROCESSING	
tpwr	55	lb	1.00
pw	5.0	wtfile	
dl	0	proc	ft
tof	0	fn	not used
nt	2048	math	f
ct	1452		
alock	n	werr	
gain	not used	wexp	
FLAGS		wbs	
il	n	wnt	
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-101.5		
wp	14636.8		
vs	111		
sc	0		
wc	250		
hzmm	58.55		
is	500.00		
rfl	6626.1		
rfp	5810.0		
th	4		
ins	100.000		
ai no ph			





1.149-*exo*

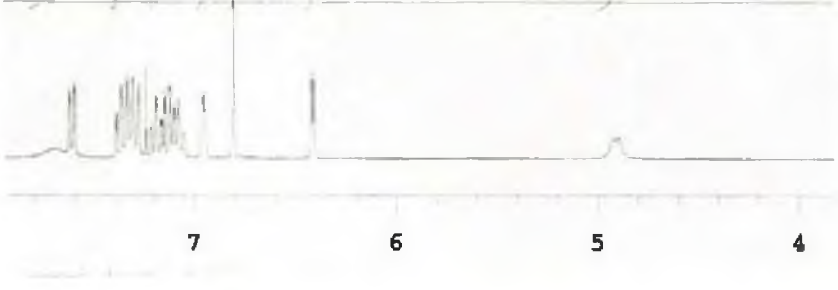
^{13}C NMR, 75 MHz, $CDCl_3$

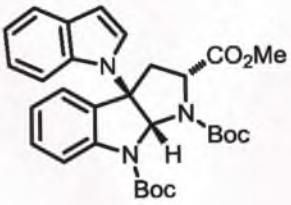


UofUtah Unity300 NMR
STANDARD 1H OBSERVE

exp2 s2pul 1026

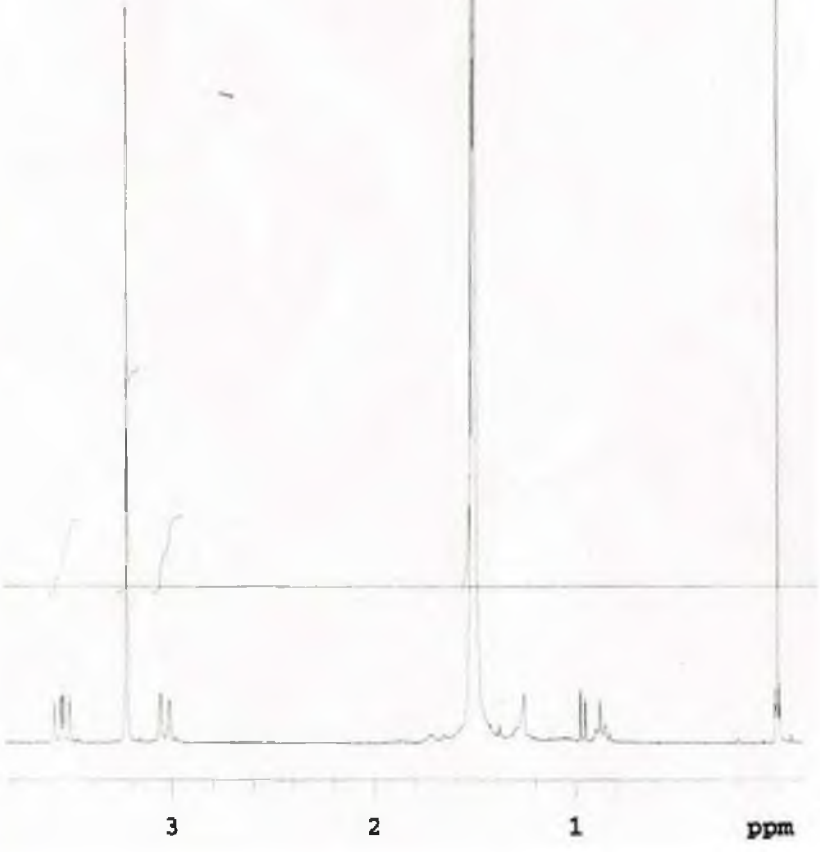
SAMPLE		SPECIAL	
date	May 11 2008	temp	not used
solvent	CDCl3	gain	10
file	exp	spin	20
ACQUISITION		hst	0.008
sw	5499.8	pw90	10.600
at	11.637	alfa	20.000
np	128000	FLAGS	
fb	3000	il	n
bs	4	in	n
d1	0	dp	y
nt	8	hs	nn
ct	8	PROCESSING	
TRANSMITTER		fn	not used
tn	H1	DISPLAY	
sfrq	300.078	sp	-38.2
tof	0	wp	2440.4
tpwr	60	rf1	1676.8
pw	5.500	rfp	0
DECOUPLER		rp	88.0
dn	H1	lp	-41.5
dof	0	PLOT	
dm	nnn	wc	250
dmm	c	sc	0
dpwr	0	vs	200
dmf	200	th	2
		ai cdc ph	

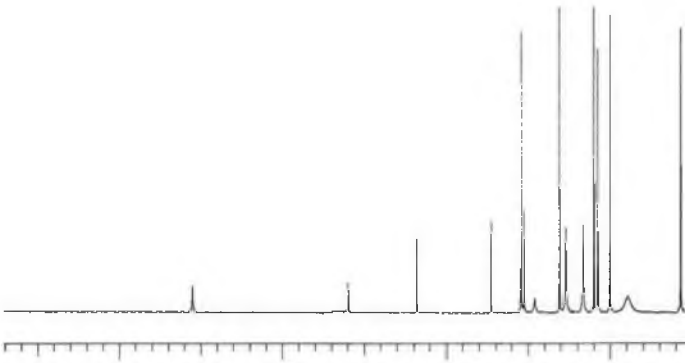


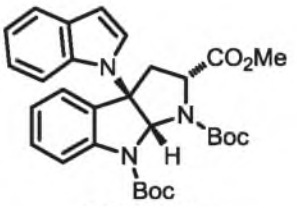


1.149-*endo*

^{1}H NMR, 300 MHz, $CDCl_3$

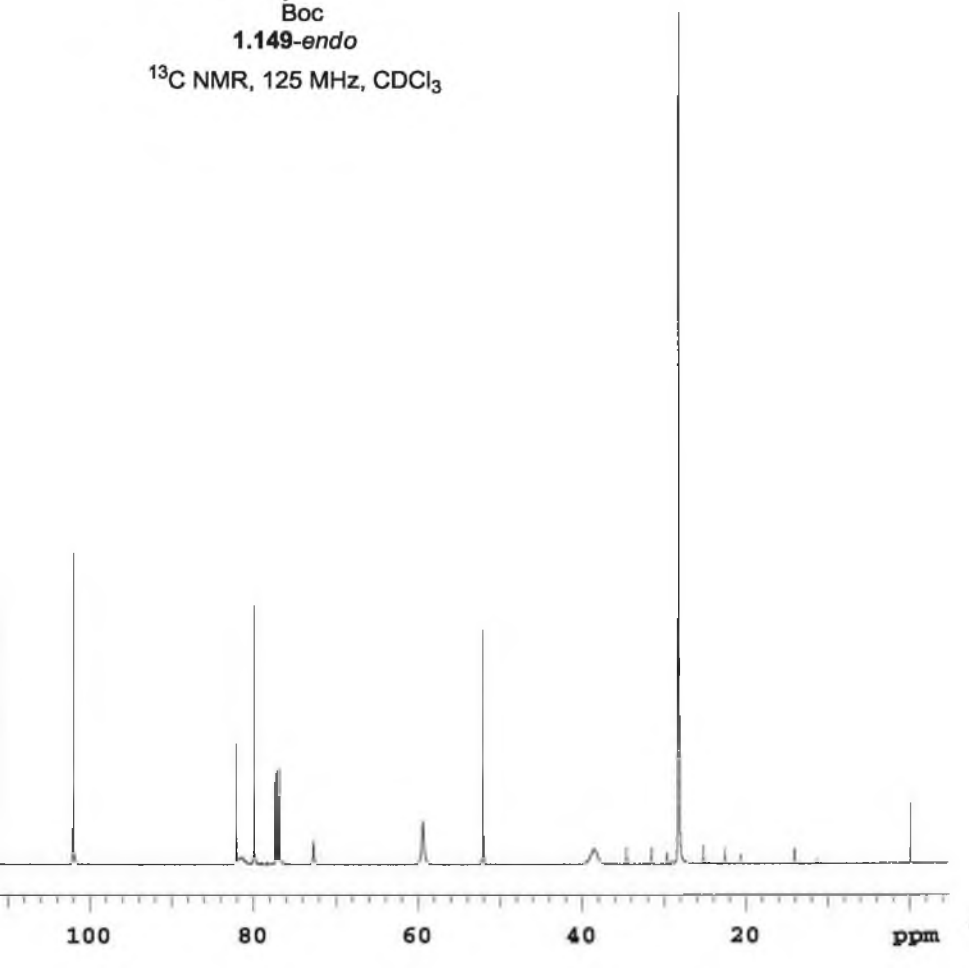



180
160
140
120



1.149-*endo*

^{13}C NMR, 125 MHz, $CDCl_3$



UofUtah Unity300 NMR
STANDARD 1H OBSERVE

exp1 s2pul 29.1a

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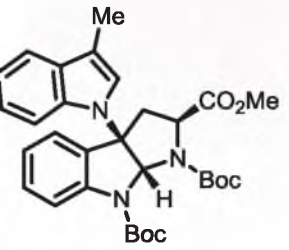
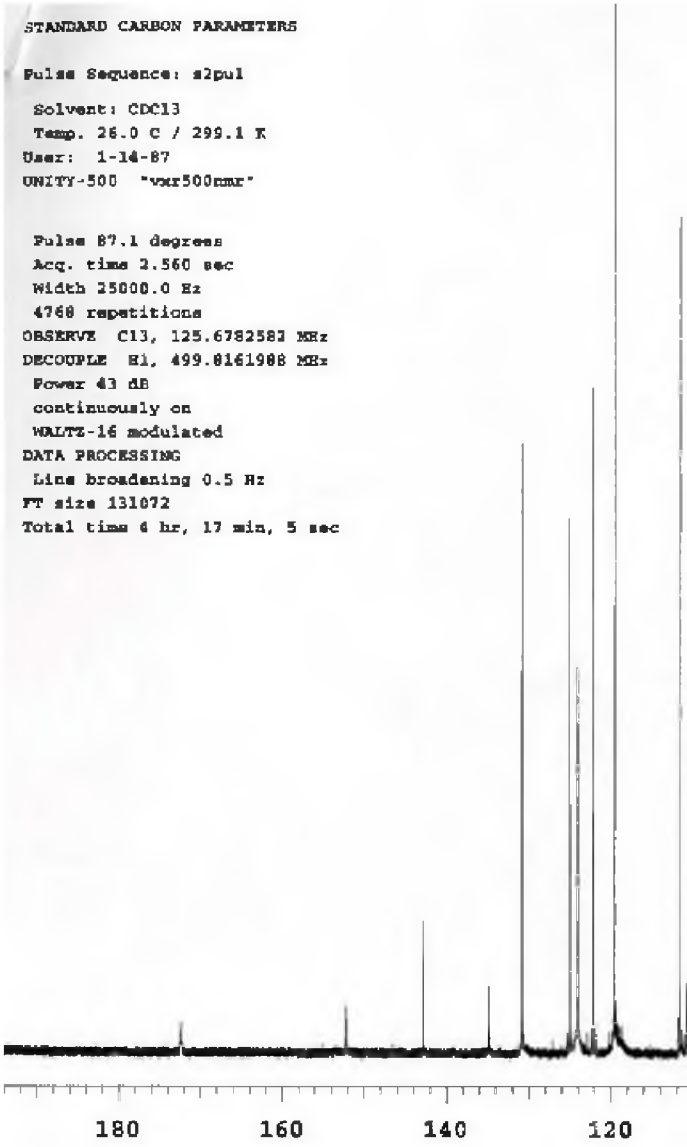
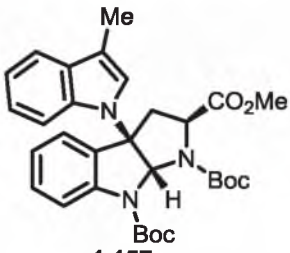
solvent	CDCl3	gain	10
file	exp	spin	20
ACQUISITION		hst	0.008
sw	5499.8	pw90	10.600
at	11.637	alfa	20.000
np	128000	FLAGS	
fb	3000	il	n
bs	4	in	n
dl	0	dp	y
nt	8	hs	nn
ct	8	PROCESSING	
TRANSMITTER		fn	not used
tn	H1	DISPLAY	
sfrq	300.078	sp	-57.5
tof	0	wp	2494.1
tpwr	60	rfl	1675.1
pw	5.500	rfp	0
DECOUPLER		rp	-108.8
dn	H1	lp	-59.5
dof	0	PLOT	
dm	nnn	wc	250
dmm	c	sc	0
dpwr	0	vs	177
dmf	200	th	2
		si cdc ph	



1.157-*exo*

^{1}H NMR, 300 MHz, $CDCl_3$


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 26.0 C / 299.1 K
User: 1-14-87
UNITY-500 "vxr500nmr"
Pulse 87.1 degrees
Acq. time 2.560 sec
Width 25000.0 Hz
4768 repetitions
OBSERVE C13, 125.6782583 MHz
DECOUPLE H1, 499.8161908 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6 hr, 17 min, 5 sec
180
160
140
120



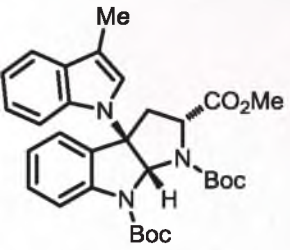
1.157-*exo*

^{13}C NMR, 125 MHz, $CDCl_3$

UofUtah Unity300 NMR
STANDARD 1E OBSERVE

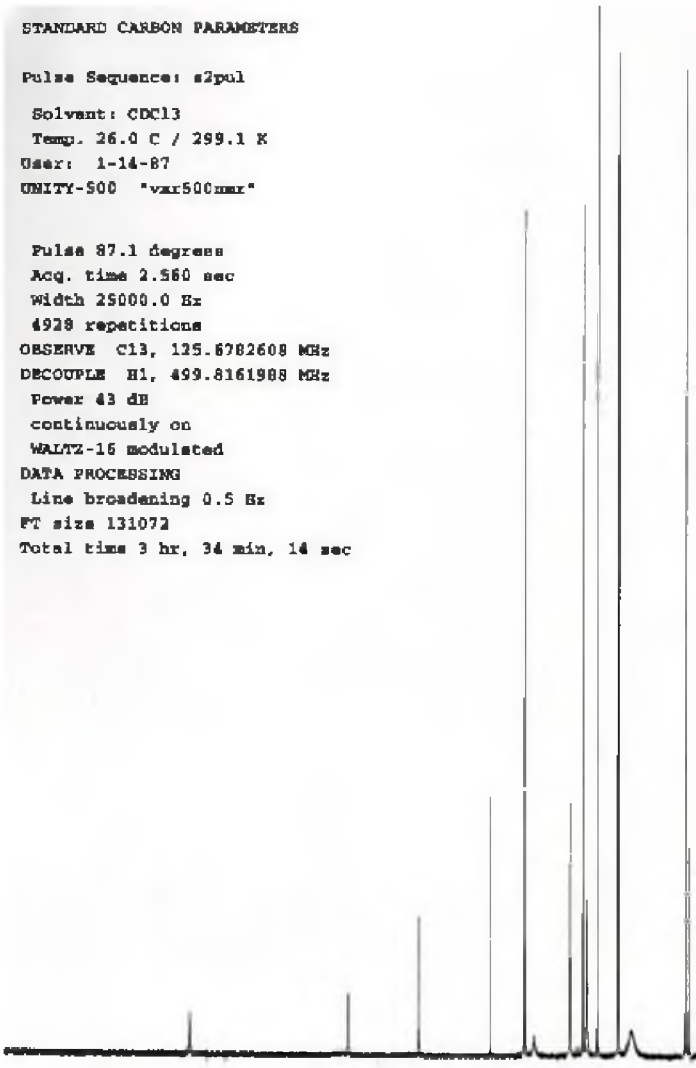
exp2 s2pul #12.2

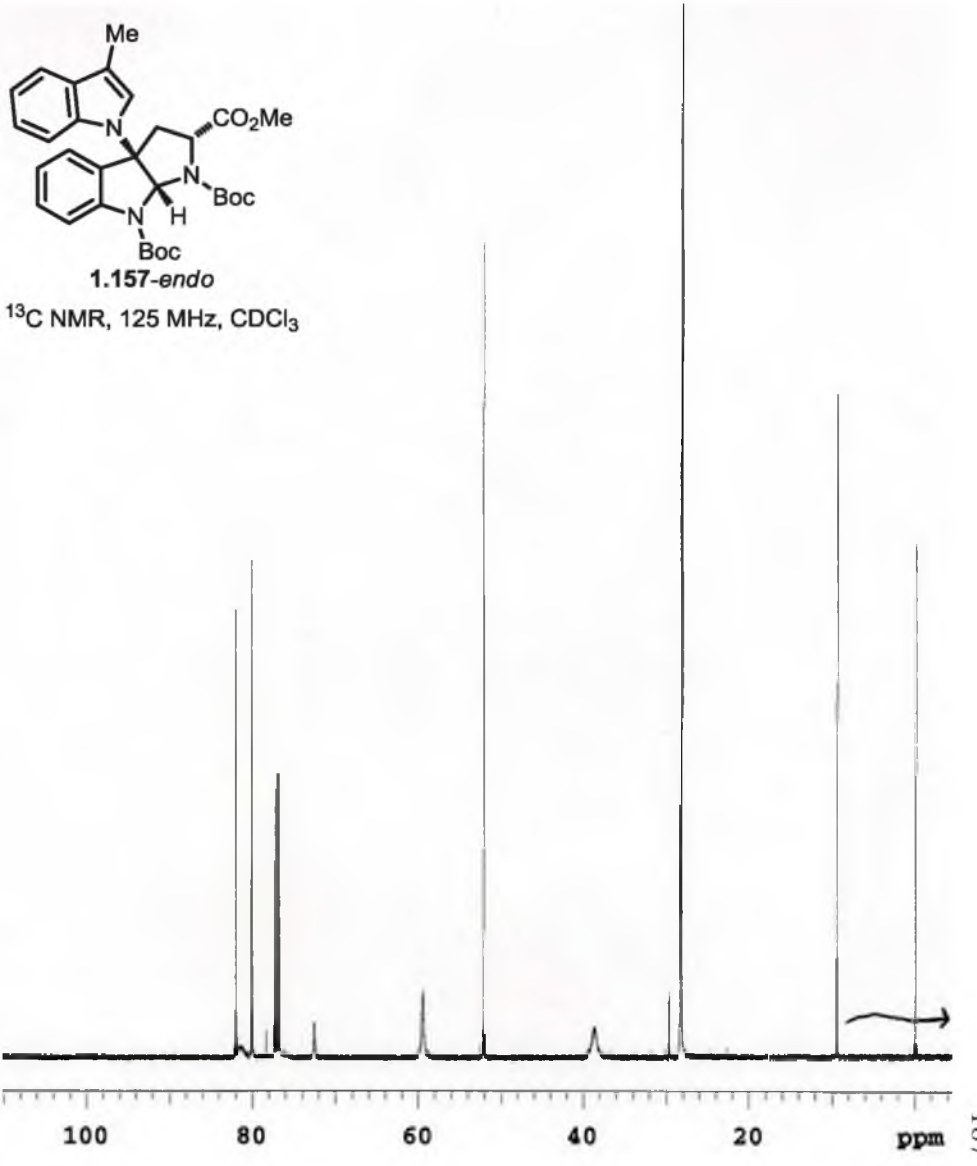
SAMPLE		SPECIAL	
date	May 10 2008	temp	not used
solvent	CDCl3	gain	10
file	exp	spin	20
ACQUISITION		hst	0.008
sw	5499.8	pw90	10.600
at	11.637	alfa	20.000
np	128000	FLAGS	
fb	3000	il	n
bs	4	in	n
d1	0	dp	y
nt	8	hs	nn
ct	8	PROCESSING	
TRANSMITTER		fn	not used
tn	H1	DISPLAY	
sfrq	300.078	sp	-101.3
tof	0	wp	2622.8
tpwr	60	rf1	1677.0
pw	5.500	rfp	0
DECOUPLER		rp	108.8
dn	H1	lp	-45.4
dof	0	PLOT	
dm	nnn	wc	250
dmm	c	sc	0
dpwr	0	vs	115
dmf	200	th	4
		ai cdc ph	



1.157-*endo*

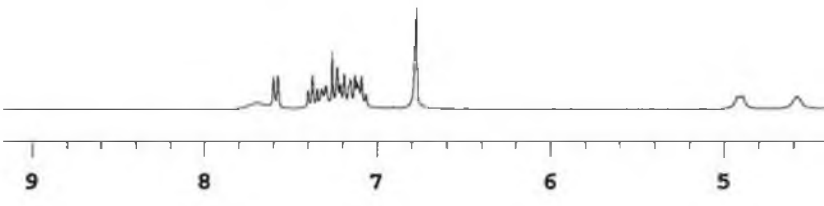
^{1}H NMR, 300 MHz, $CDCl_3$

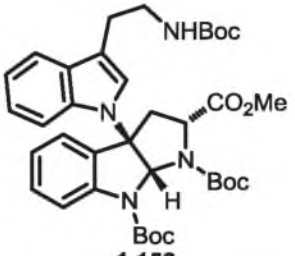

STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 26.0 C / 299.1 K
User: 1-14-87
UNITY-500 "vxr500nmr"
Pulse 87.1 degrees
Acq. time 2.560 sec
Width 25000.0 Hz
4928 repetitions
OBSERVE C13, 125.6782608 MHz
DECOUPLE H1, 499.8161988 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 3 hr, 34 min, 14 sec
180
160
140
120



1.157-*endo*

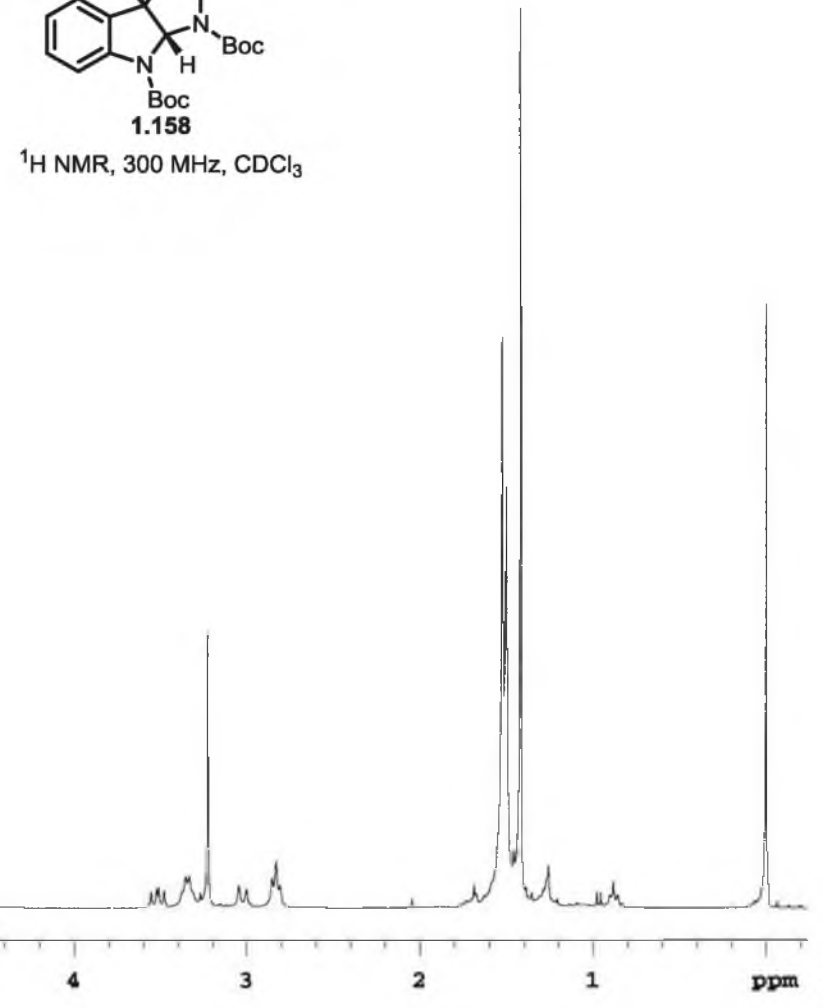
^{13}C NMR, 125 MHz, $CDCl_3$

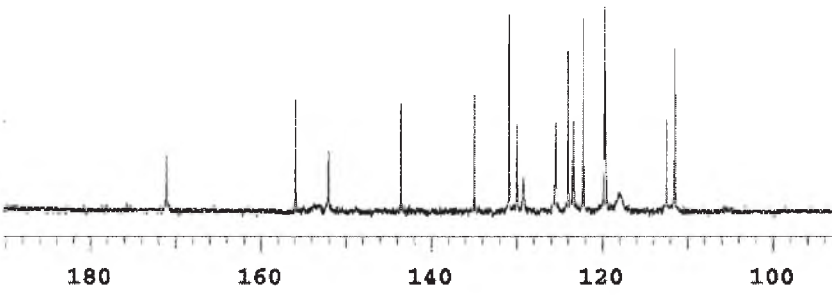

9
8
7
6
5

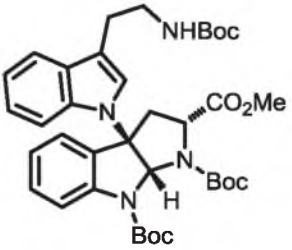


1.158

^{1}H NMR, 300 MHz, $CDCl_3$

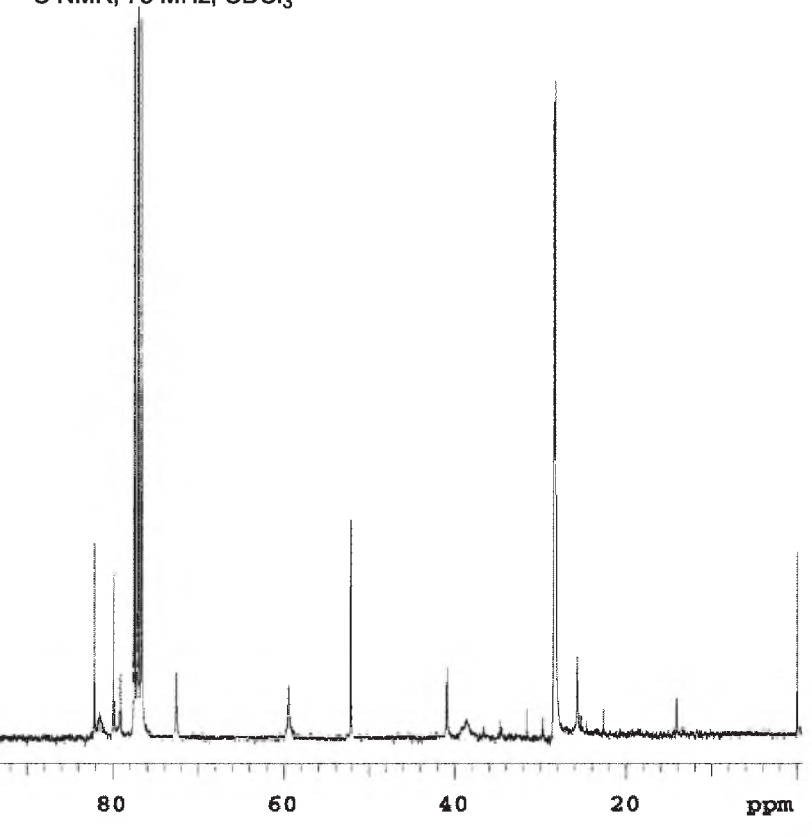


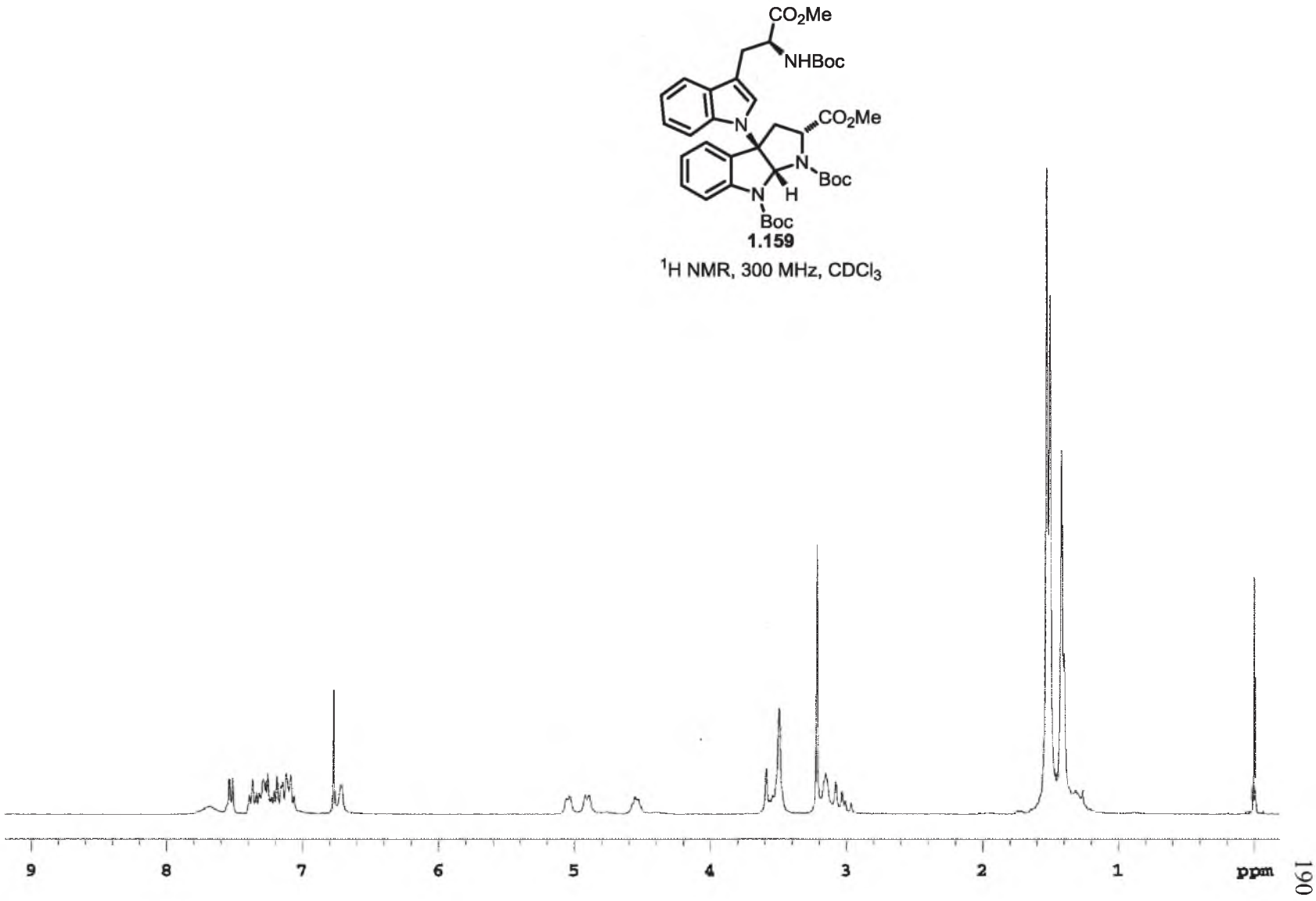

180
160
140
120
100

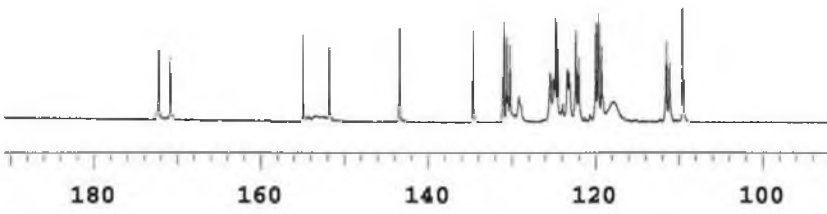


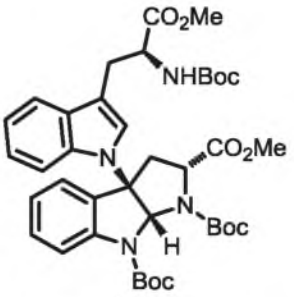
1.158

^{13}C NMR, 75 MHz, $CDCl_3$



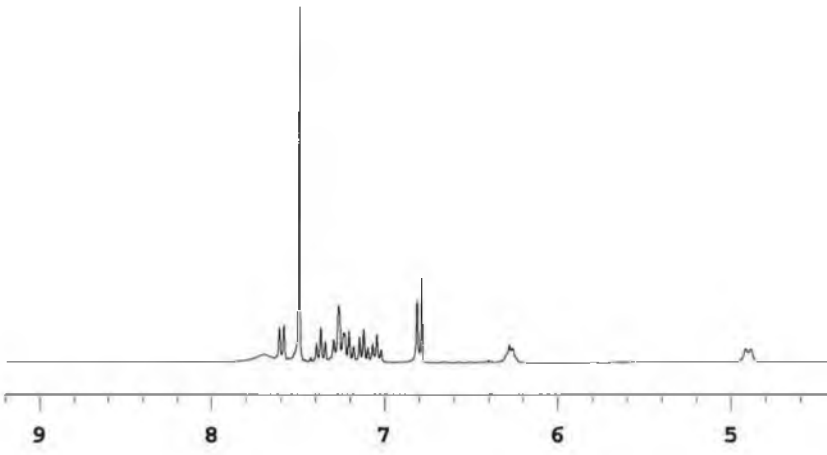

CO2Me
NHBoc
CO2Me
N
N
Boc
N
H
Boc
1.159
1H NMR, 300 MHz, CDCl3
9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100



1.159

^{13}C NMR, 125 MHz, $CDCl_3$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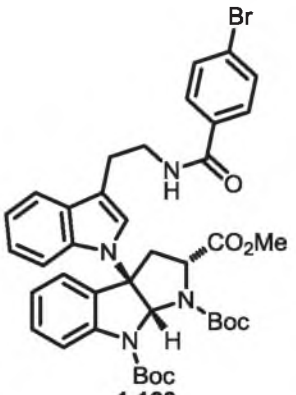
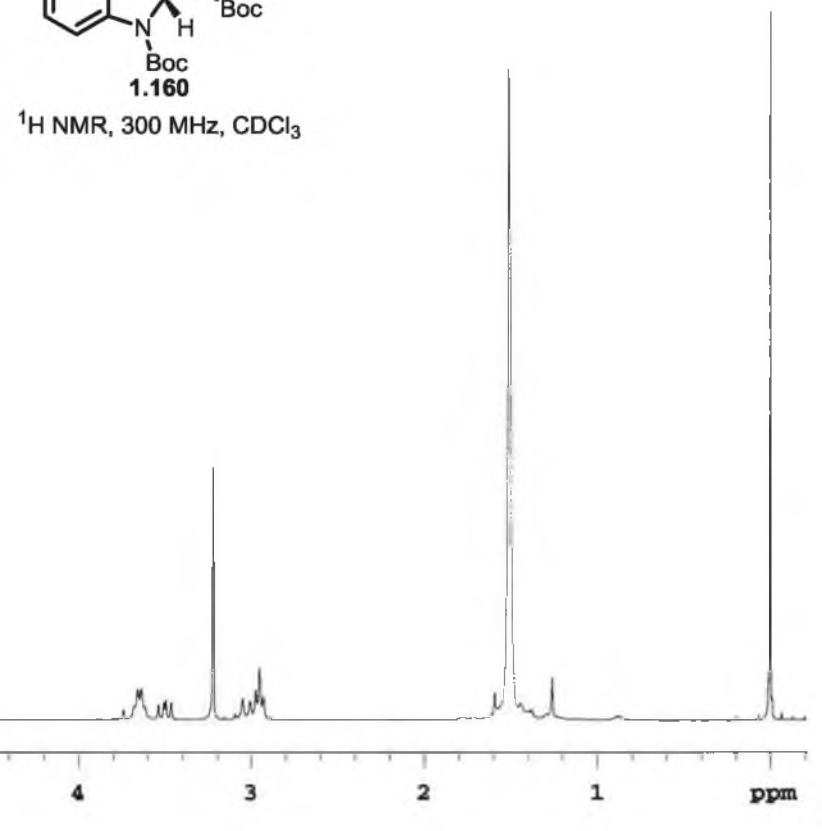
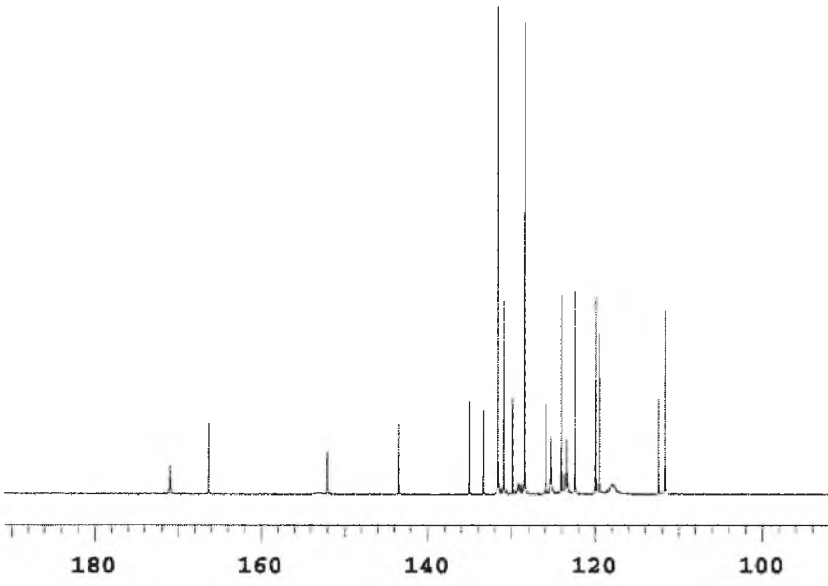


1.160

^{1}H NMR, 300 MHz, $CDCl_3$

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160
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120
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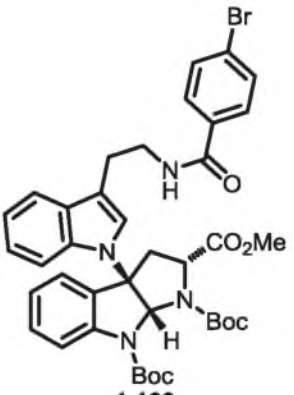
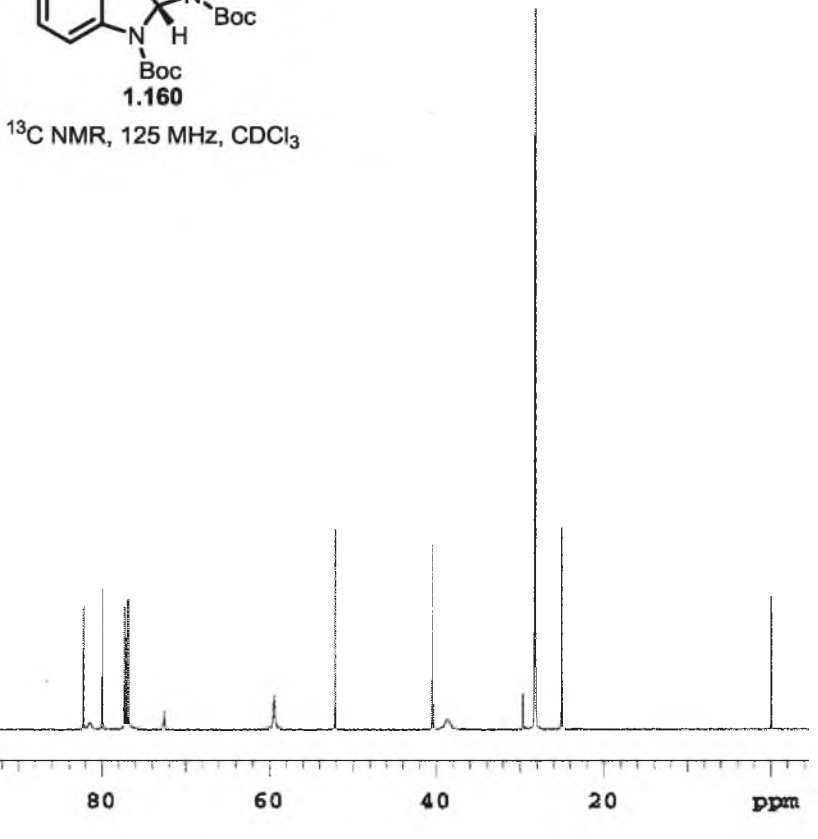
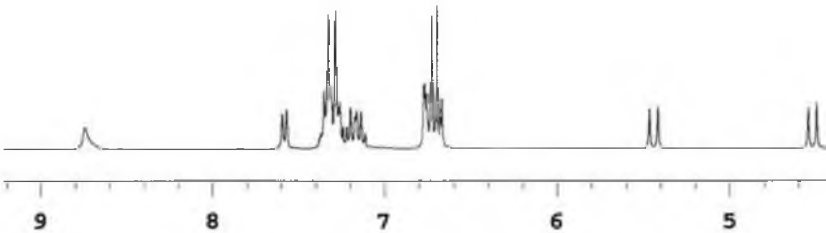


1.160

^{13}C NMR, 125 MHz, $CDCl_3$

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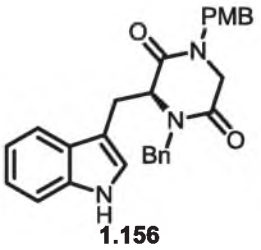
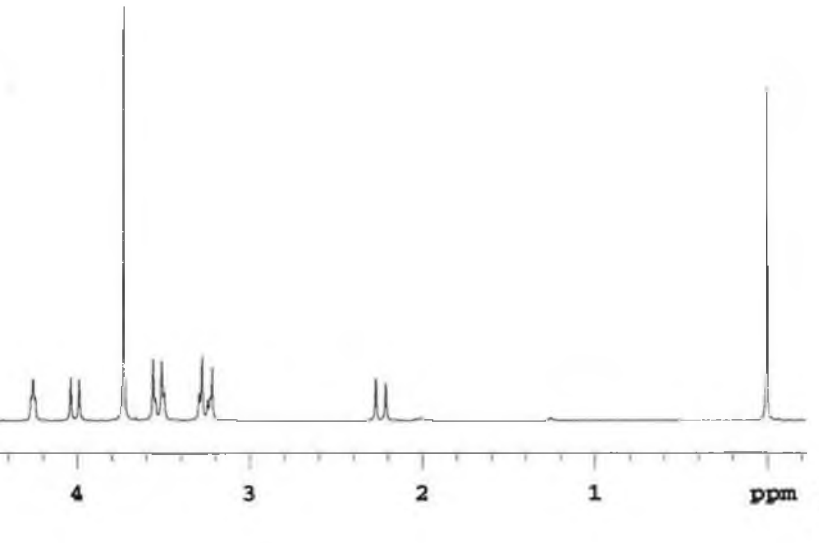
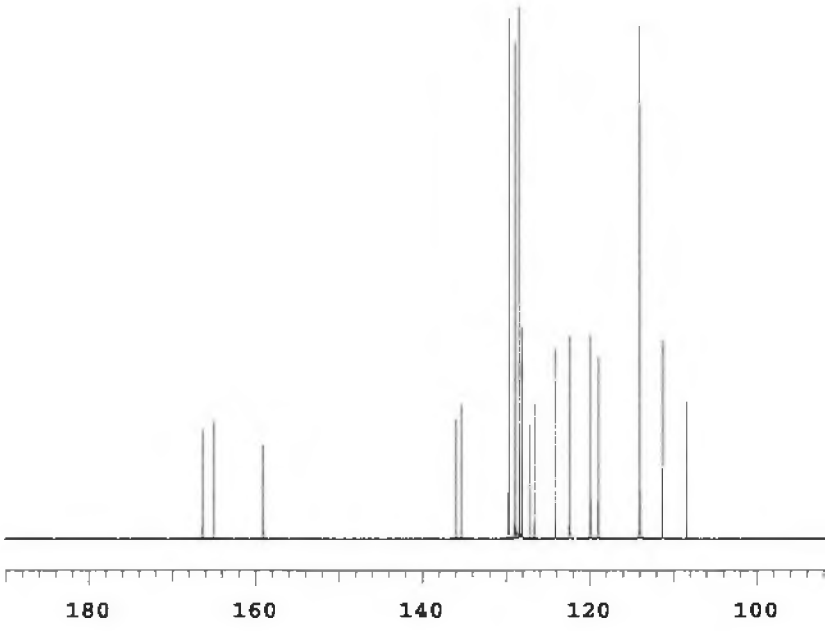
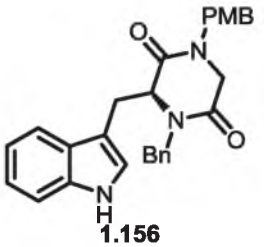


1.156

^{1}H NMR, 300 MHz, $CDCl_3$

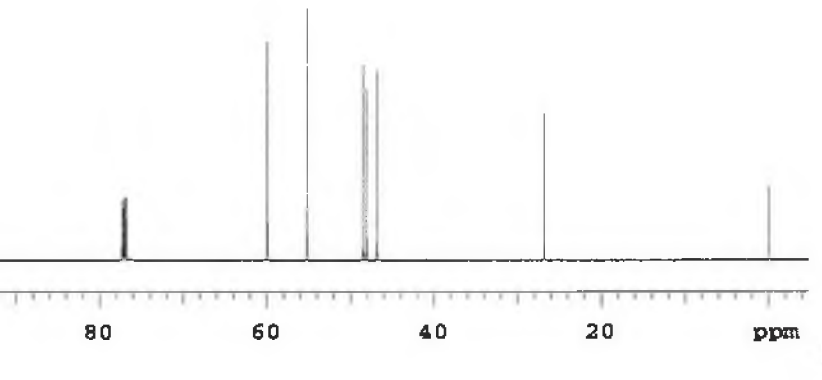



180
160
140
120
100



1.156

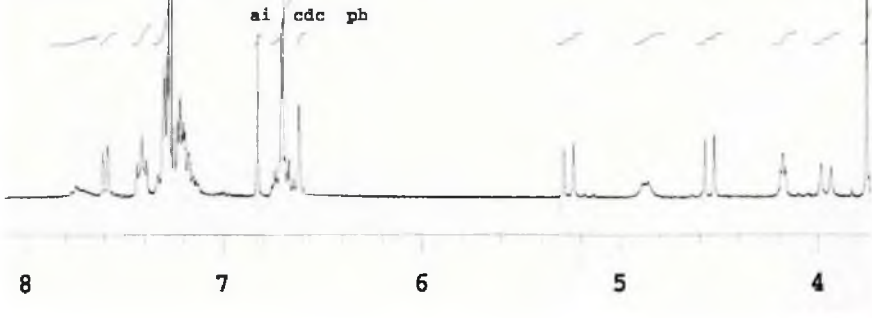
^{13}C NMR, 125 MHz, $CDCl_3$

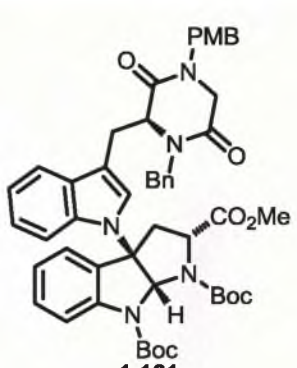


ofUtah Unity300 NMR
STANDARD 1H OBSERVE

exp3 s2pul

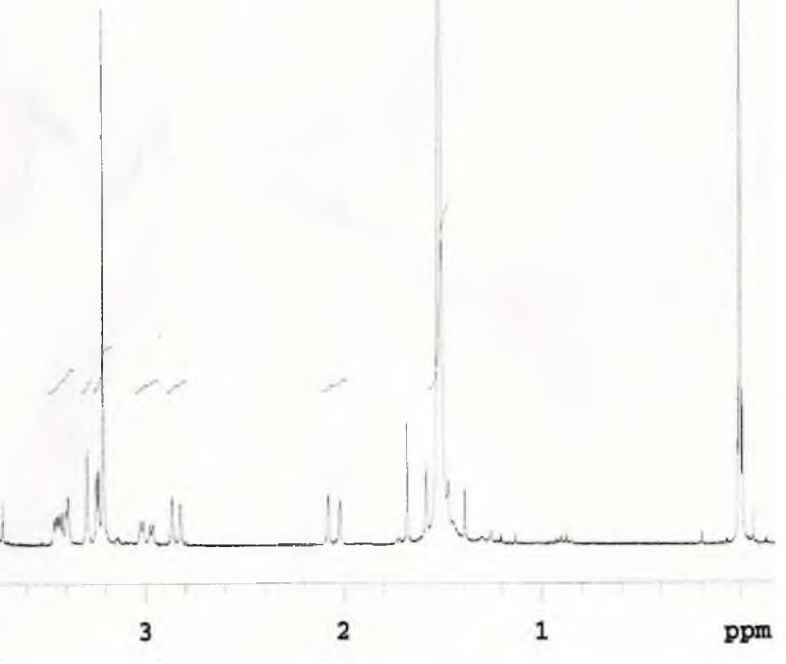
SAMPLE		SPECIAL	
date	Aug 6 2008	temp	not used
solvent	CDCl3	gain	10
file	exp	spin	20
ACQUISITION		hst	0.008
sw	5499.8	pw90	10.600
at	11.637	alfa	20.000
np	128000	FLAGS	
fb	3000	il	n
bs	4	in	n
dl	0	dp	y
nt	8	hs	nn
ct	8	PROCESSING	
TRANSMITTER		fn	not used
tn	H1	DISPLAY	
sfrq	300.078	sp	-60.8
tof	0	wp	2495.2
tpwr	60	rfl	1672.3
pw	5.500	rfp	0
DECOUPLER		rp	-111.2
dn	H1	lp	-53.7
dof	0	PLOT	
dm	nnn	wc	250
dmm	c	sc	0
dpwr	0	vs	500
dmf	200	th	2
		ai	cdc ph

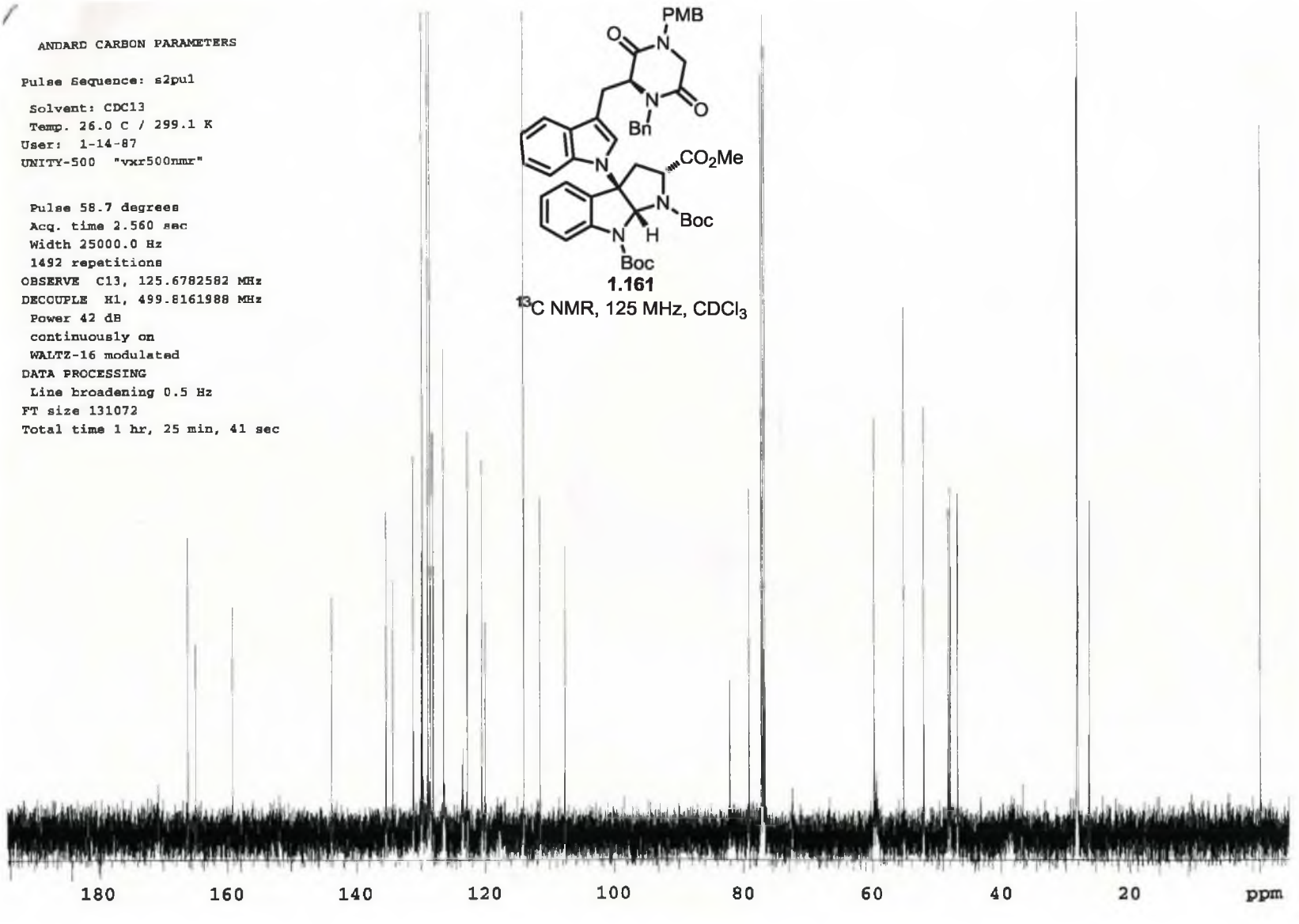


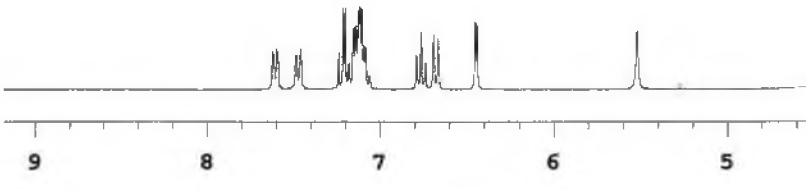


1.161

^{1}H NMR, 300 MHz, $CDCl_3$




ANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 26.0 C / 299.1 K
User: 1-14-87
UNITY-500 "vxr500nmr"
Pulse 58.7 degrees
Acq. time 2.560 sec
Width 25000.0 Hz
1492 repetitions
OBSERVE C13, 125.6782582 MHz
DECOUPLE H1, 499.8161988 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 1 hr, 25 min, 41 sec
PMB
Bn
CO2Me
Boc
Boc
1.161
13C NMR, 125 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm


9
8
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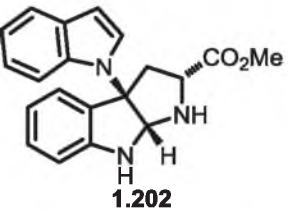
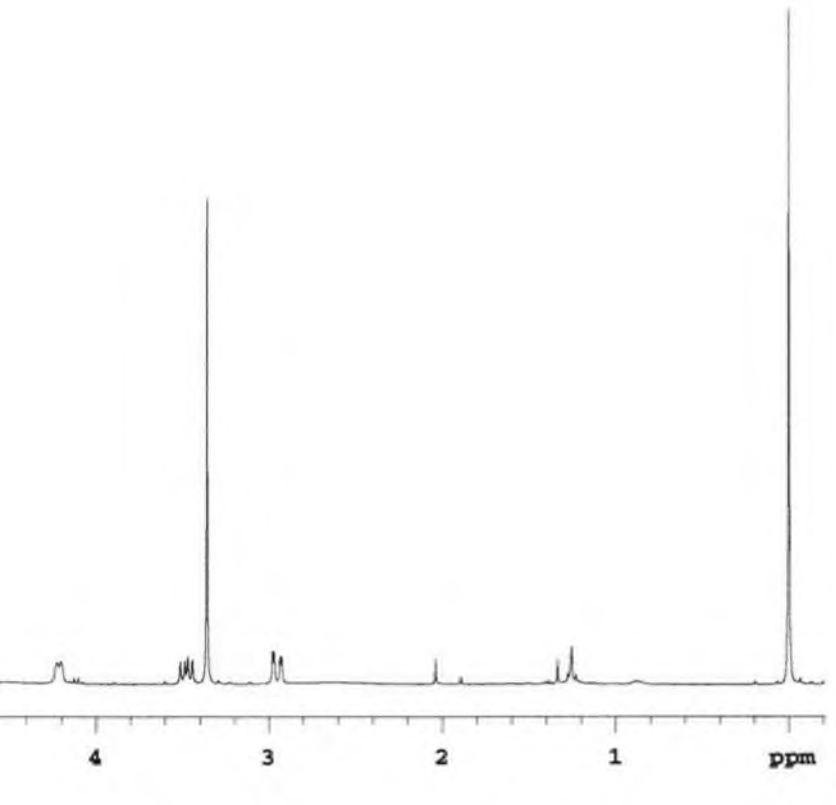
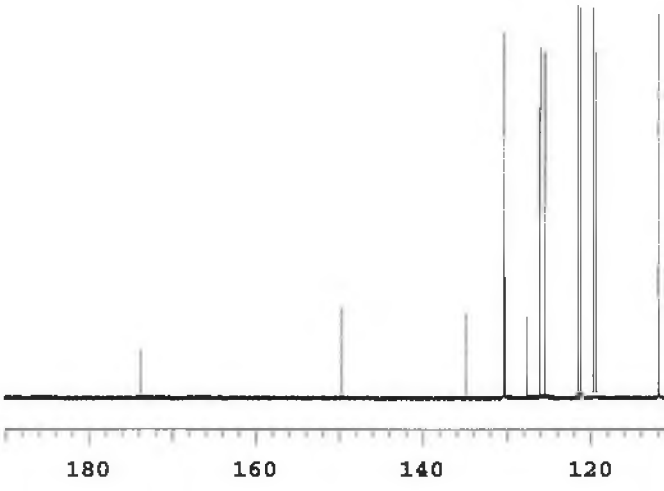
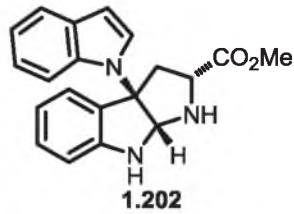


1.202

^{1}H NMR, 300 MHz, $CDCl_3$

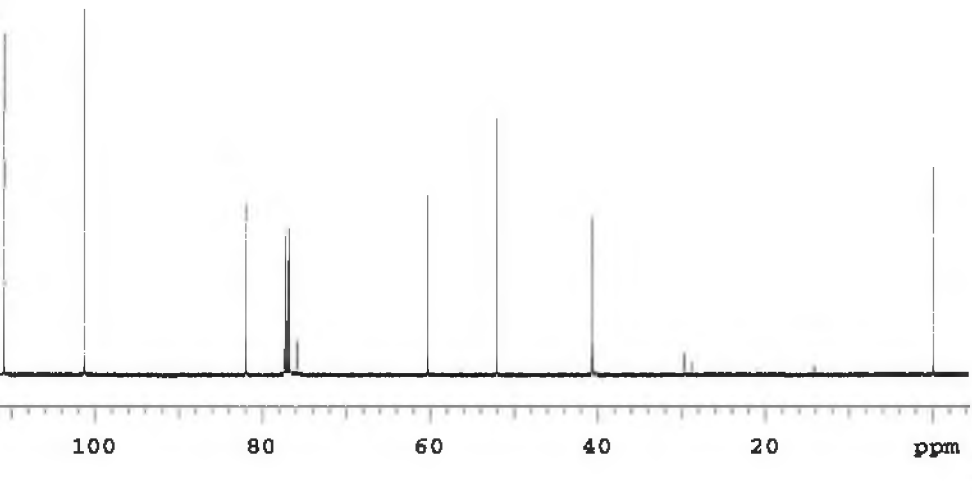


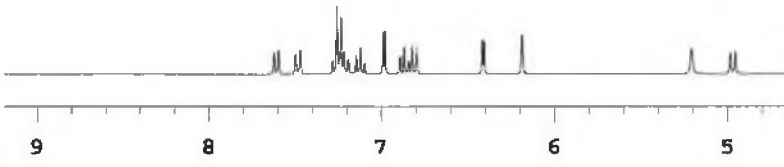

180
160
140
120



1.202

^{13}C NMR, 125 MHz, $CDCl_3$




9
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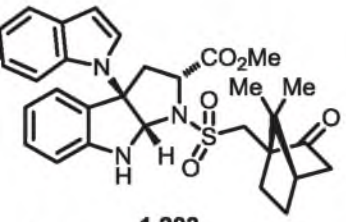
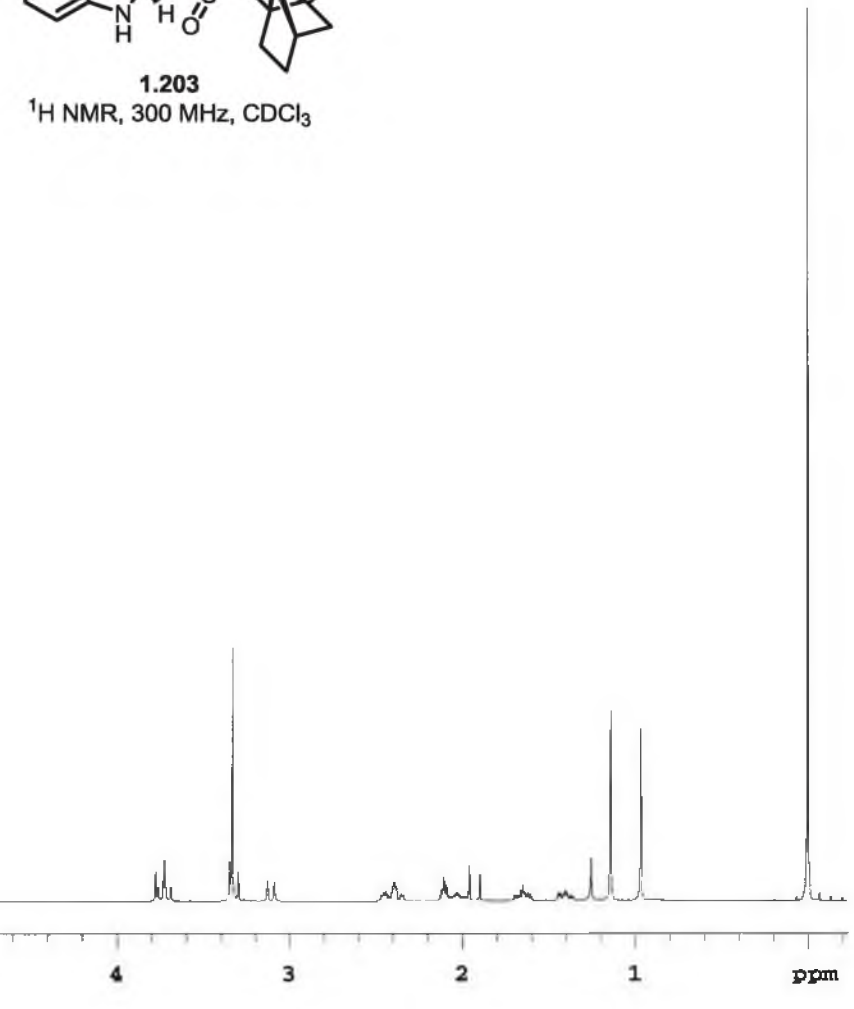
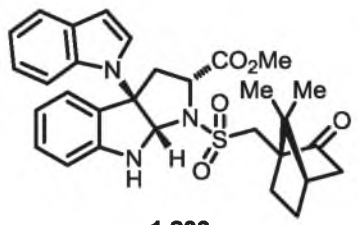


1.203

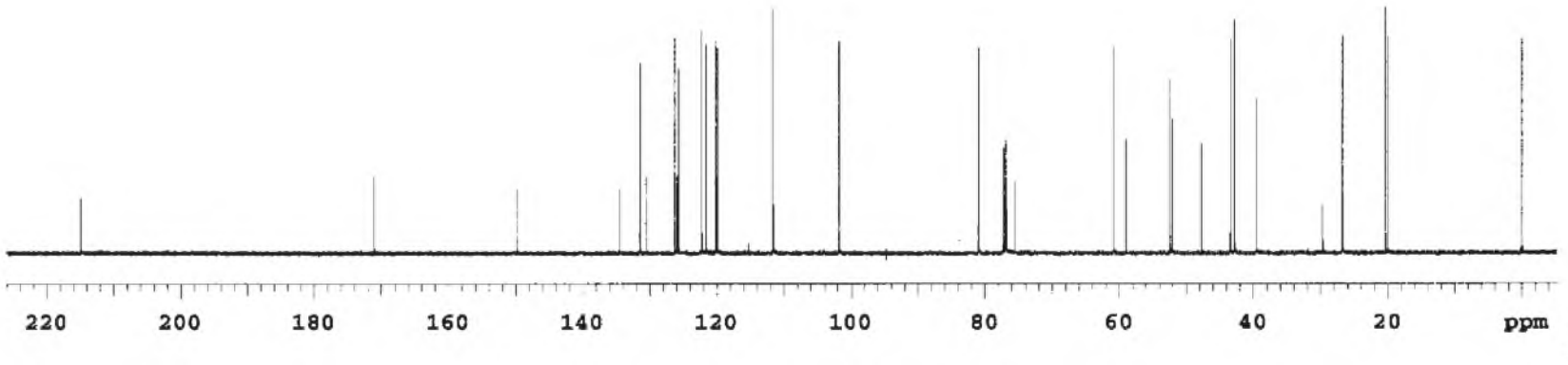
^{1}H NMR, 300 MHz, $CDCl_3$

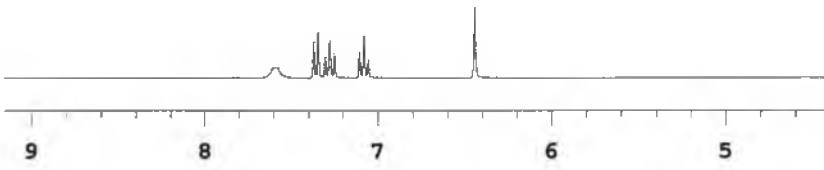




1.203

^{13}C NMR, 125 MHz, $CDCl_3$




9
8
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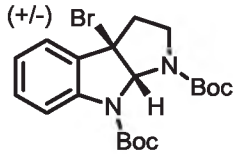
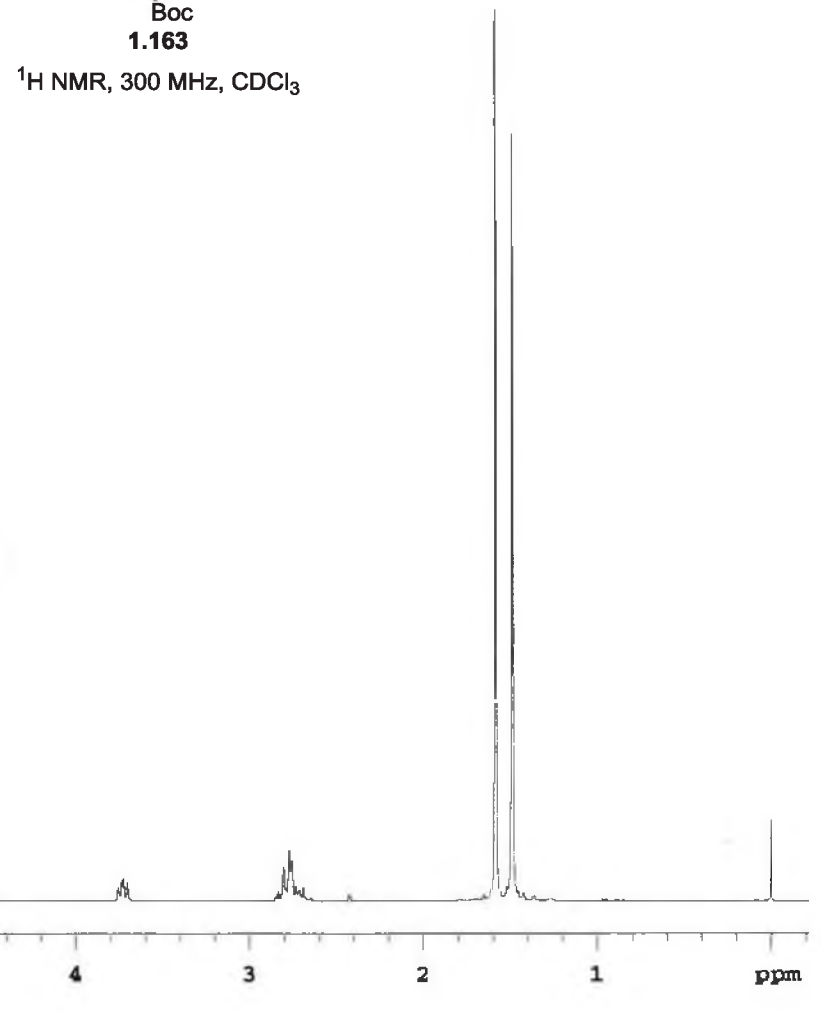
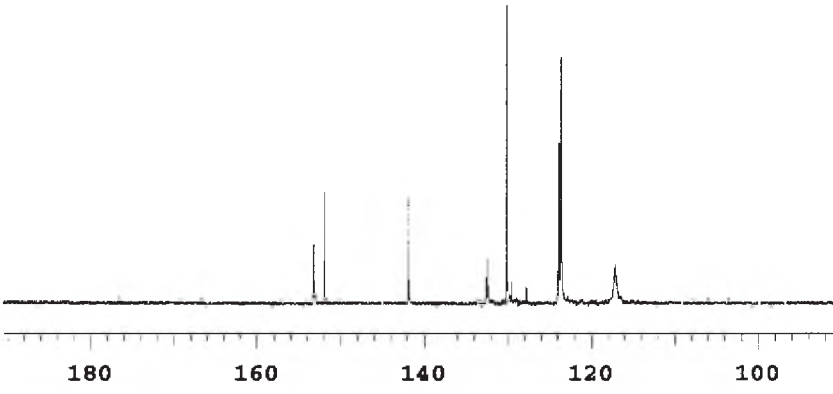
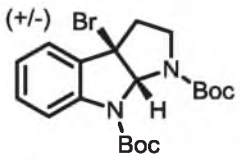


1.163

^{1}H NMR, 300 MHz, $CDCl_3$

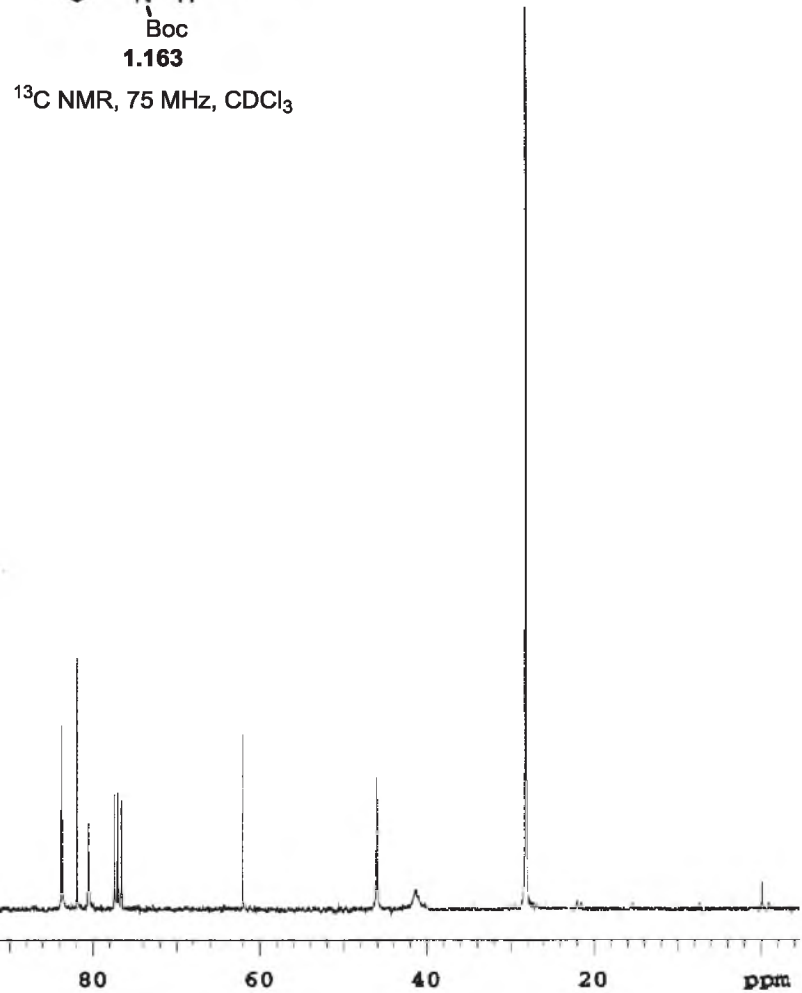


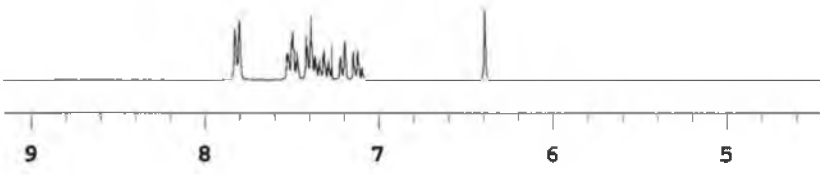

180
160
140
120
100



1.163

^{13}C NMR, 75 MHz, $CDCl_3$




9
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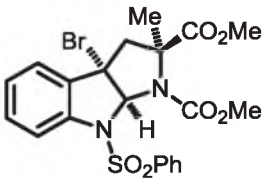
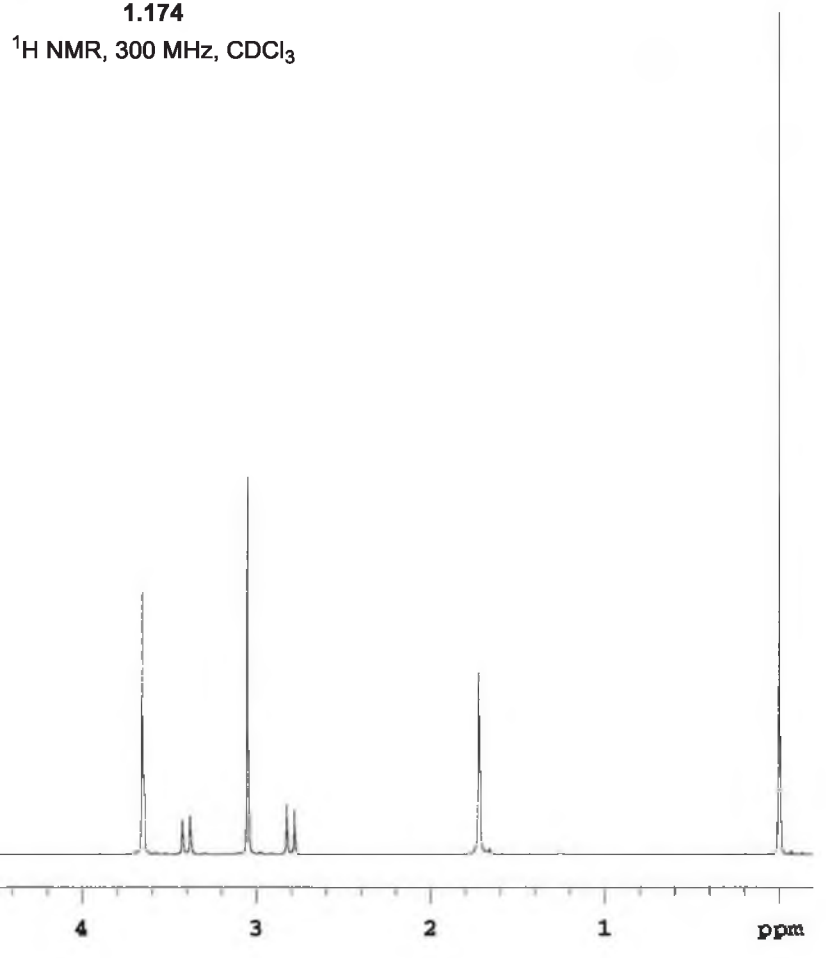
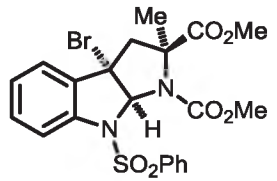


1.174

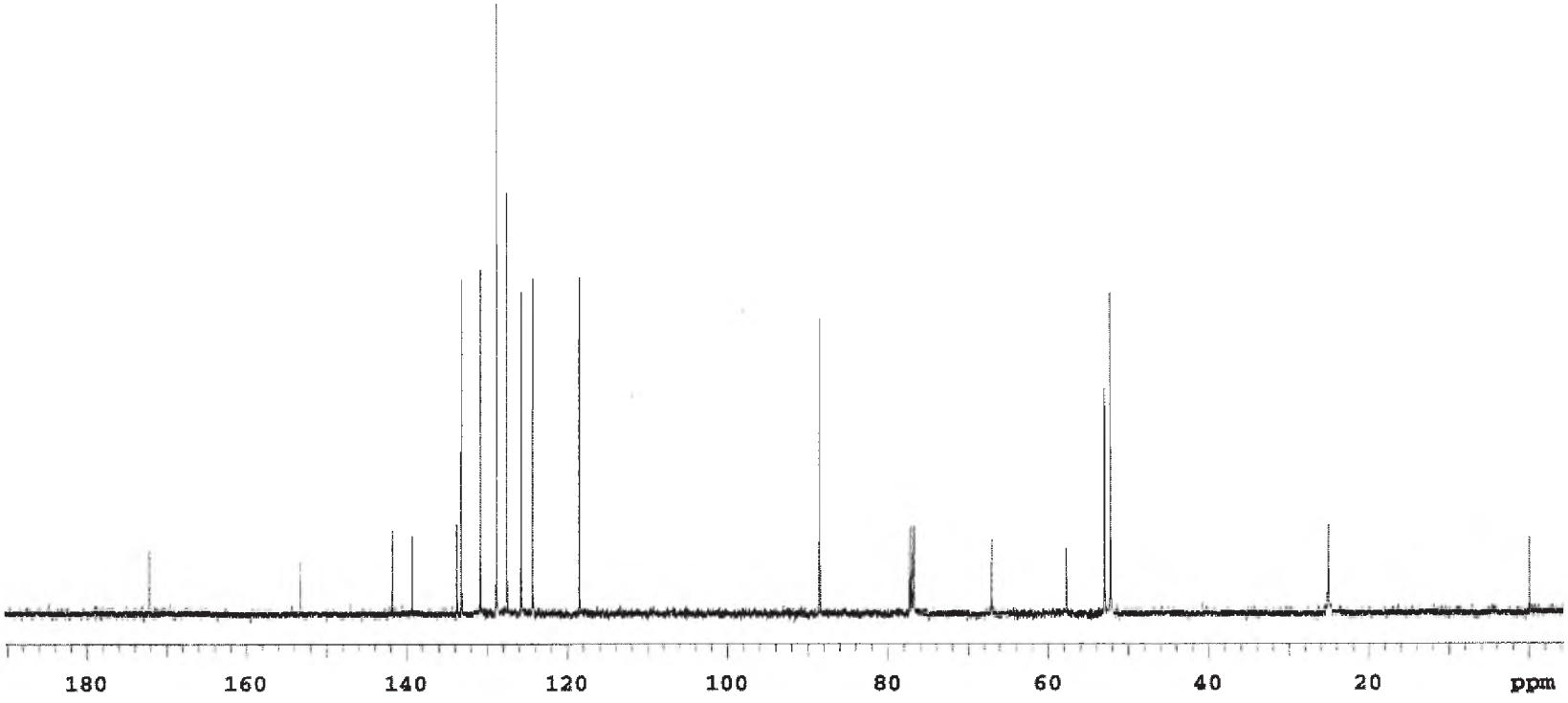
^{1}H NMR, 300 MHz, $CDCl_3$

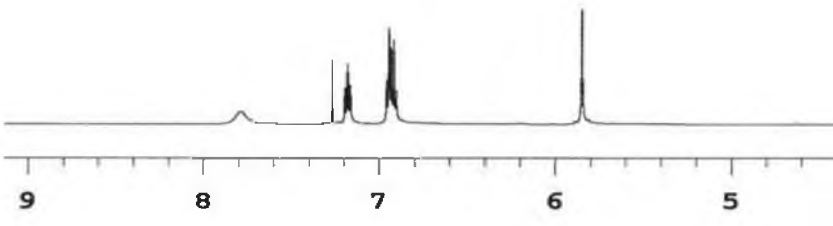




1.174

^{13}C NMR, 125 MHz, $CDCl_3$

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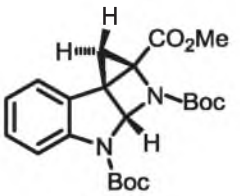
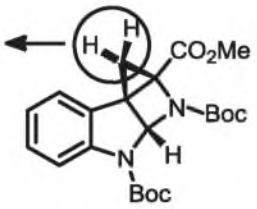


1.170

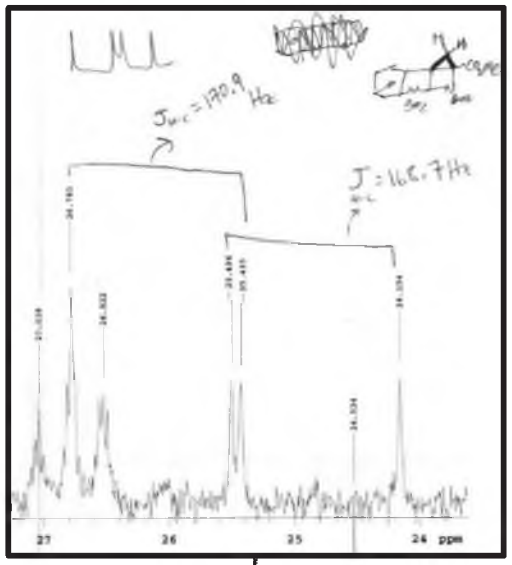
^{1}H NMR, 500 MHz, $CDCl_3$

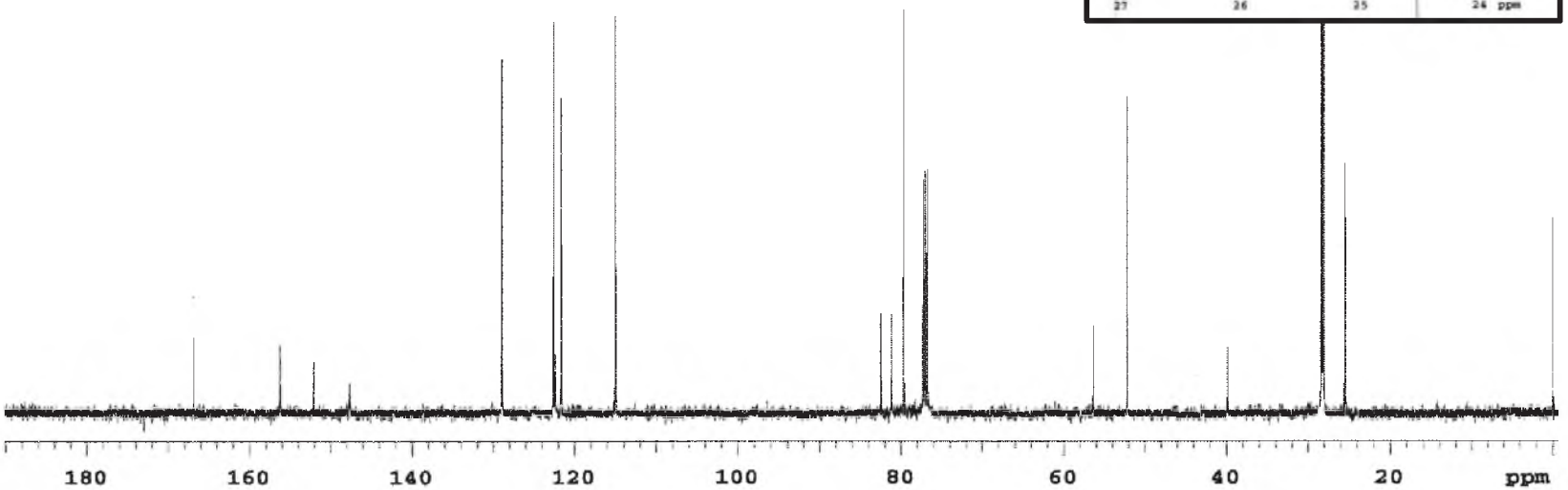
Carbon-Proton Coupled Spectra
(shown in inset)

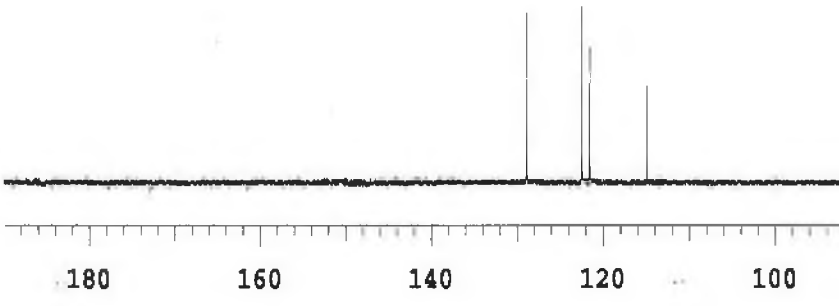


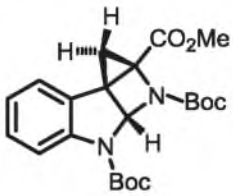
1.170

^{13}C NMR, 125 MHz, $CDCl_3$



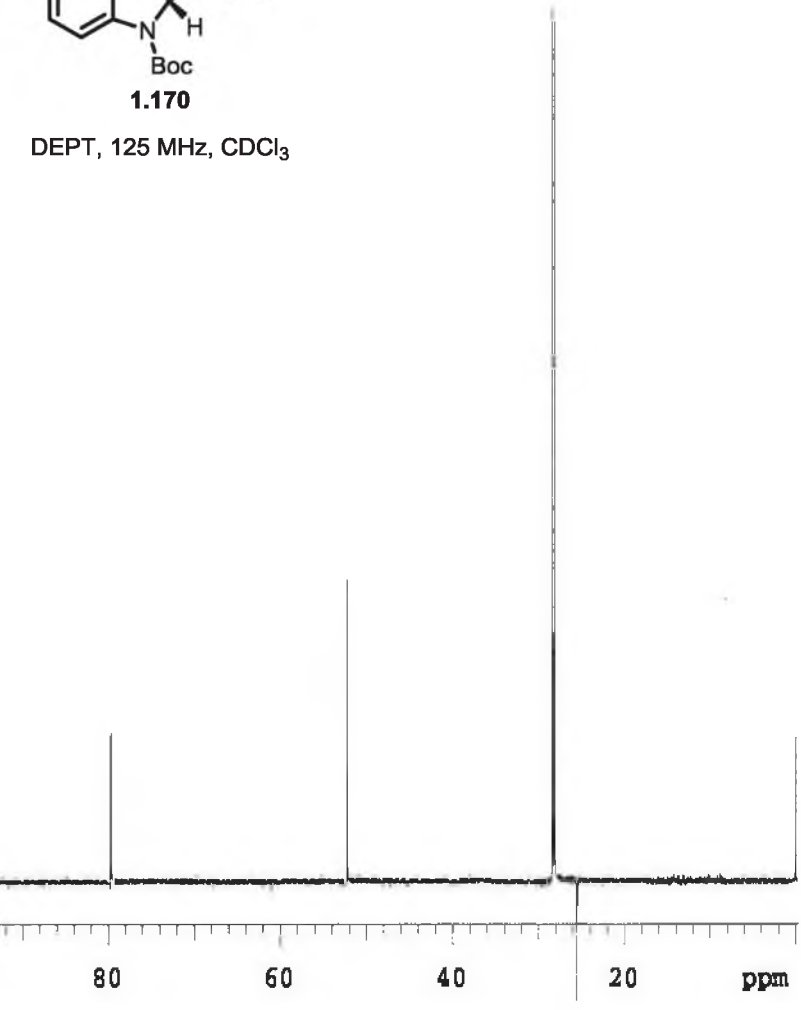


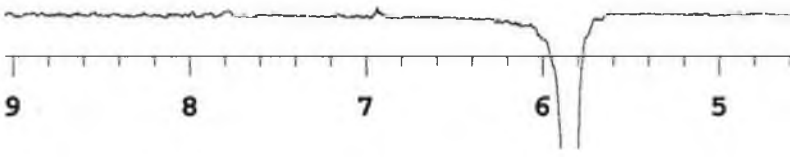

180
160
140
120
100



1.170

DEPT, 125 MHz, $CDCl_3$




9
8
7
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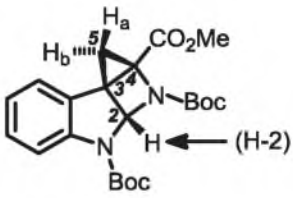
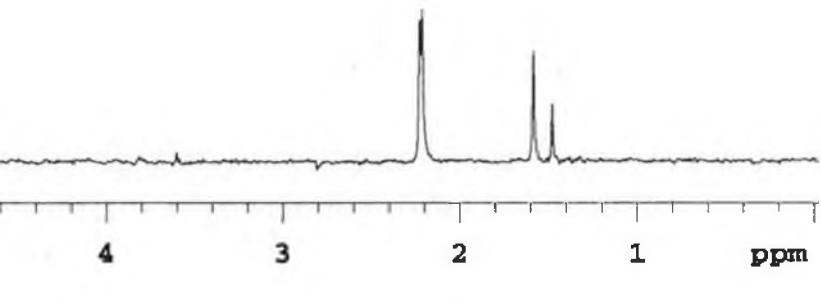
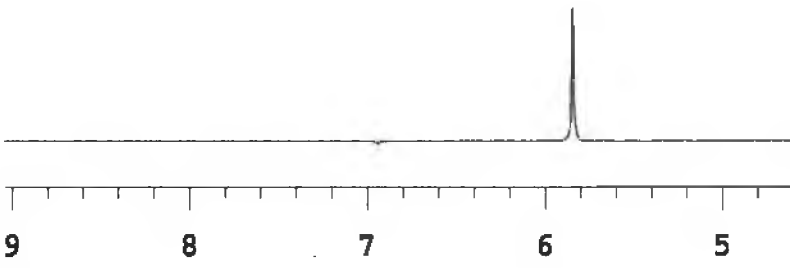
5



1.170

nOe, 500 MHz, $CDCl_3$
Irradiation of H-2

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8
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6
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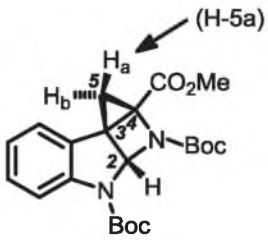
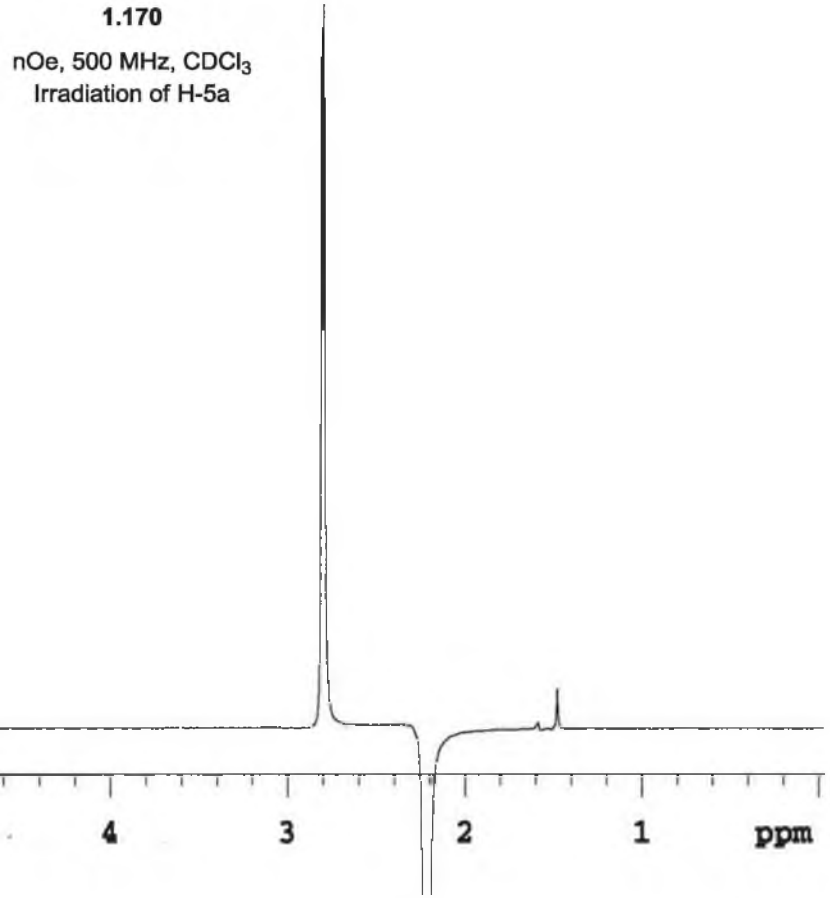
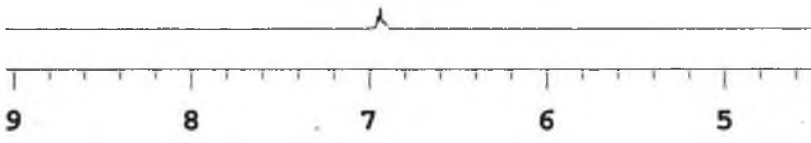


1.170

nOe, 500 MHz, $CDCl_3$
Irradiation of H-5a

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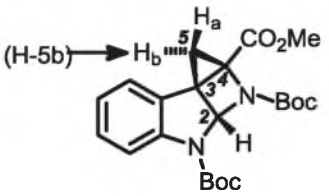
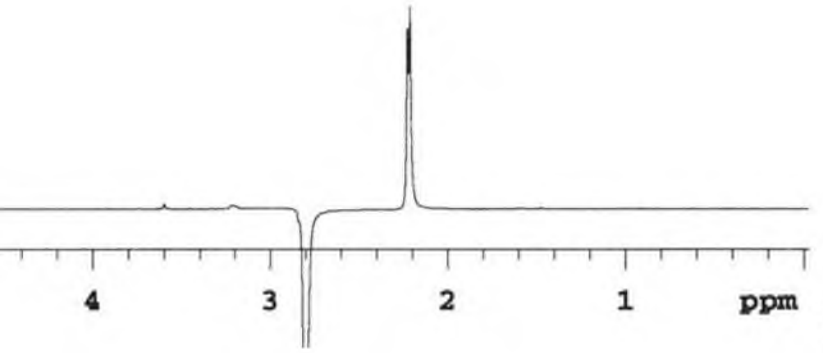
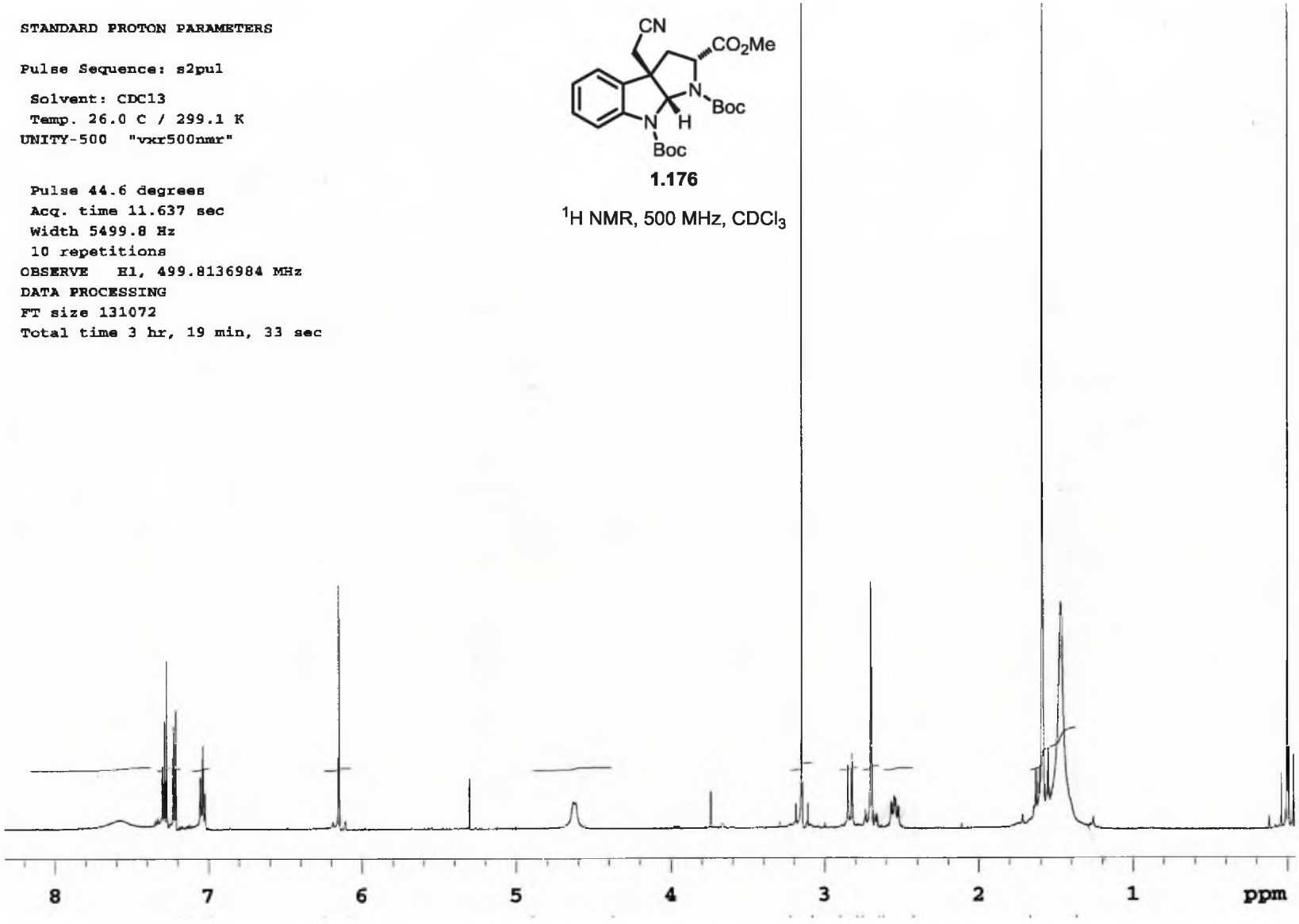
8
7
6
5

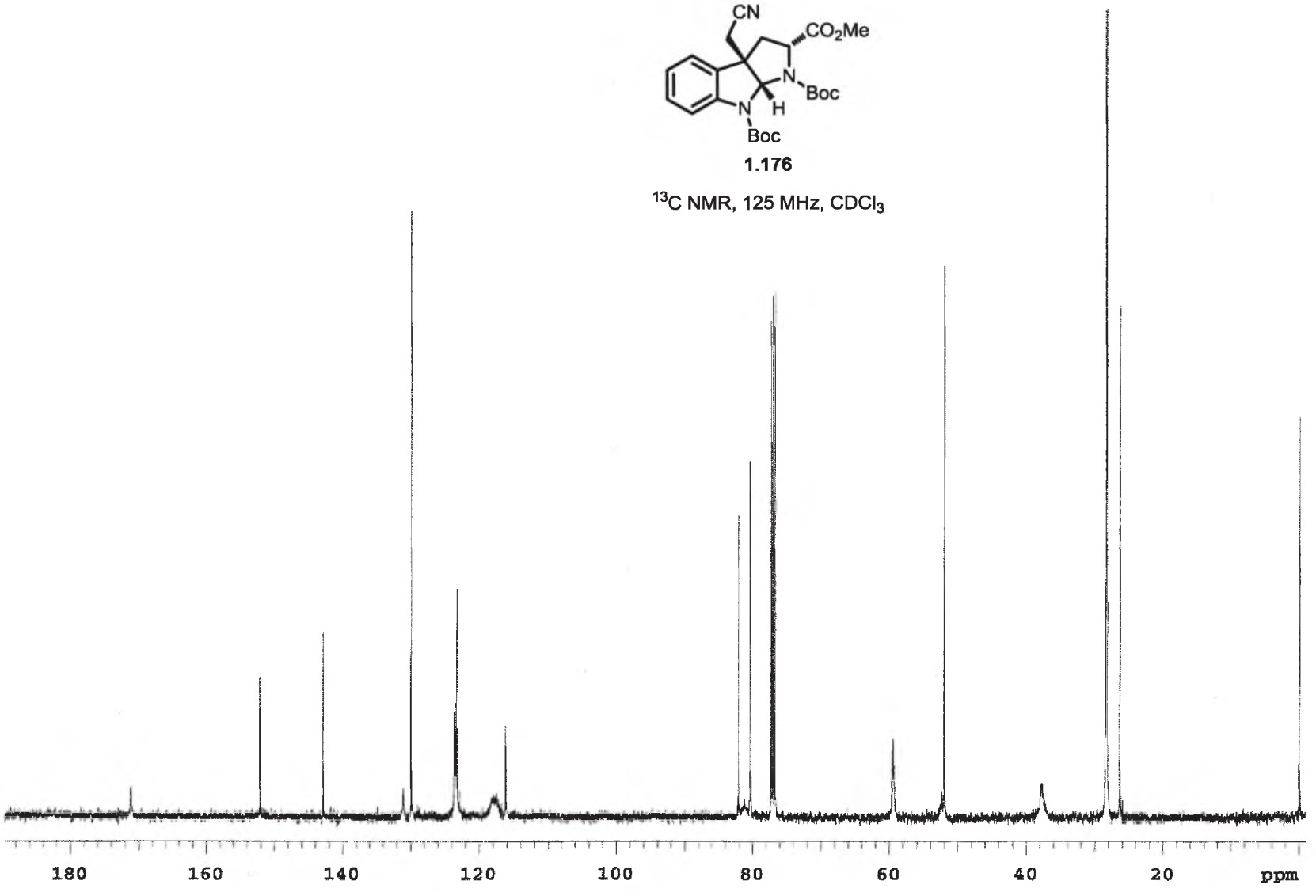


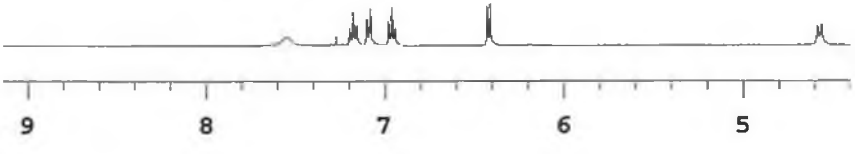
1.170

nOe, 500 MHz, $CDCl_3$
Irradiation of H-5b




STANDARD PROTON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 26.0 C / 299.1 K
UNITY-500 "vxr500nmr"
Pulse 44.6 degrees
Acq. time 11.637 sec
Width 5499.8 Hz
10 repetitions
OBSERVE H1, 499.8136984 MHz
DATA PROCESSING
FT size 131072
Total time 3 hr, 19 min, 33 sec
CN
CO2Me
N
Boc
N
H
Boc
1.176
1H NMR, 500 MHz, CDCl3
8
7
6
5
4
3
2
1
ppm


CN
CO2Me
N
Boc
N
H
Boc
1.176
13C NMR, 125 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm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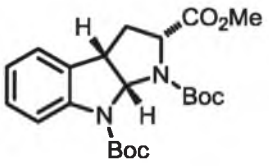
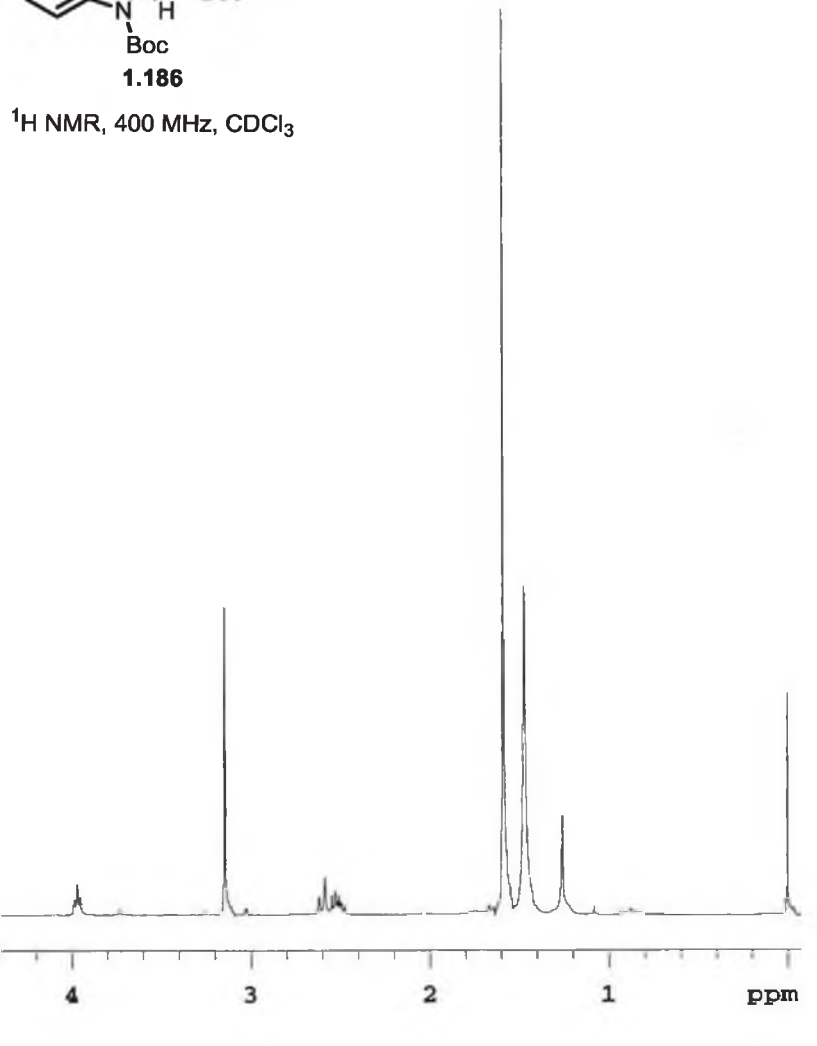
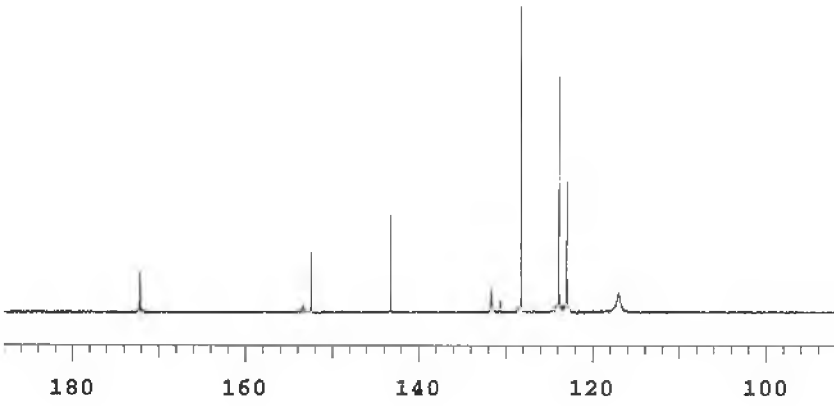
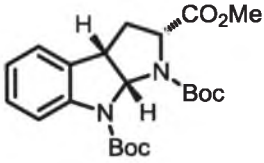


1.186

^{1}H NMR, 400 MHz, $CDCl_3$

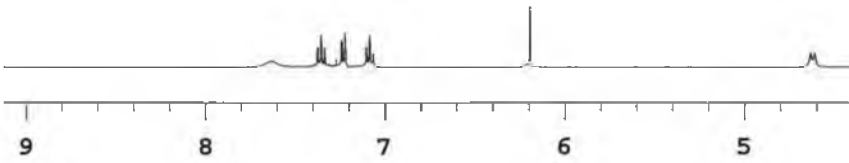



180
160
140
120
100



1.186

^{13}C NMR, 100 MHz, $CDCl_3$


9
8
7
6
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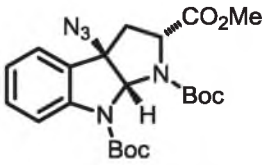
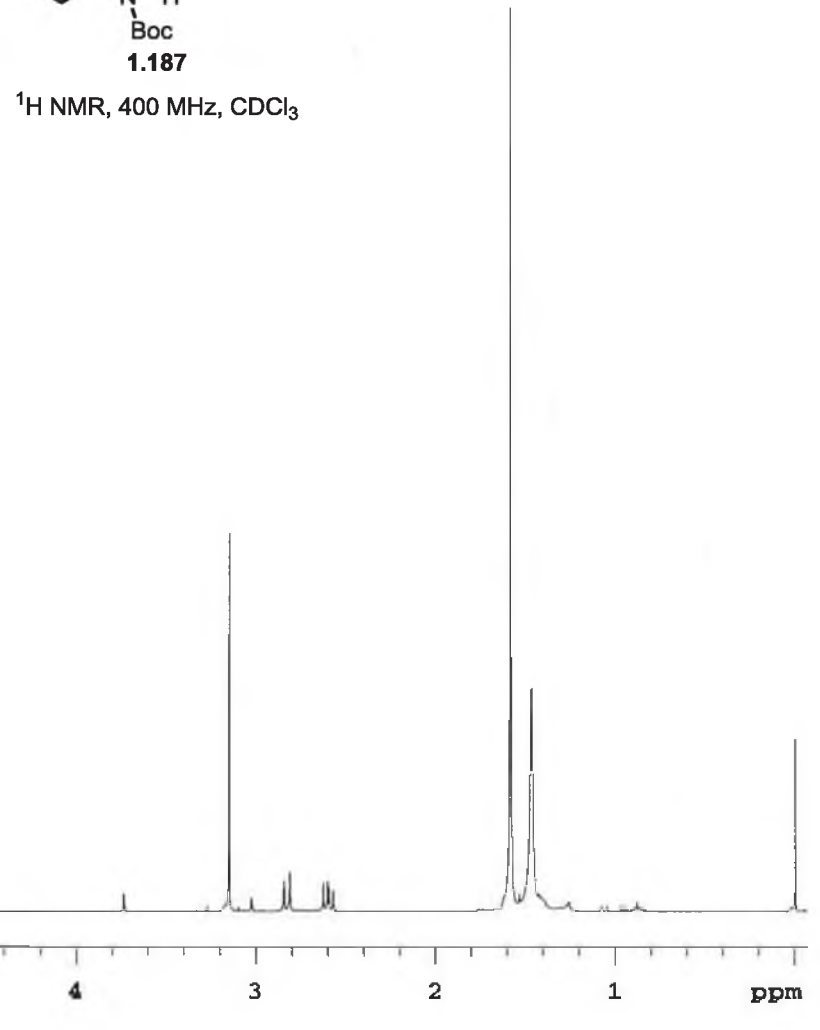
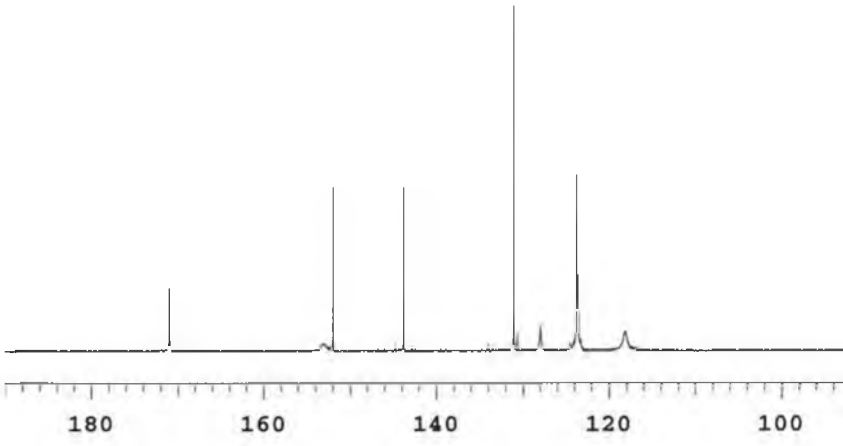
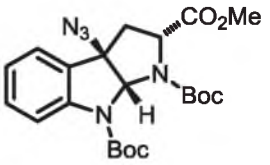


1.187

^{1}H NMR, 400 MHz, $CDCl_3$

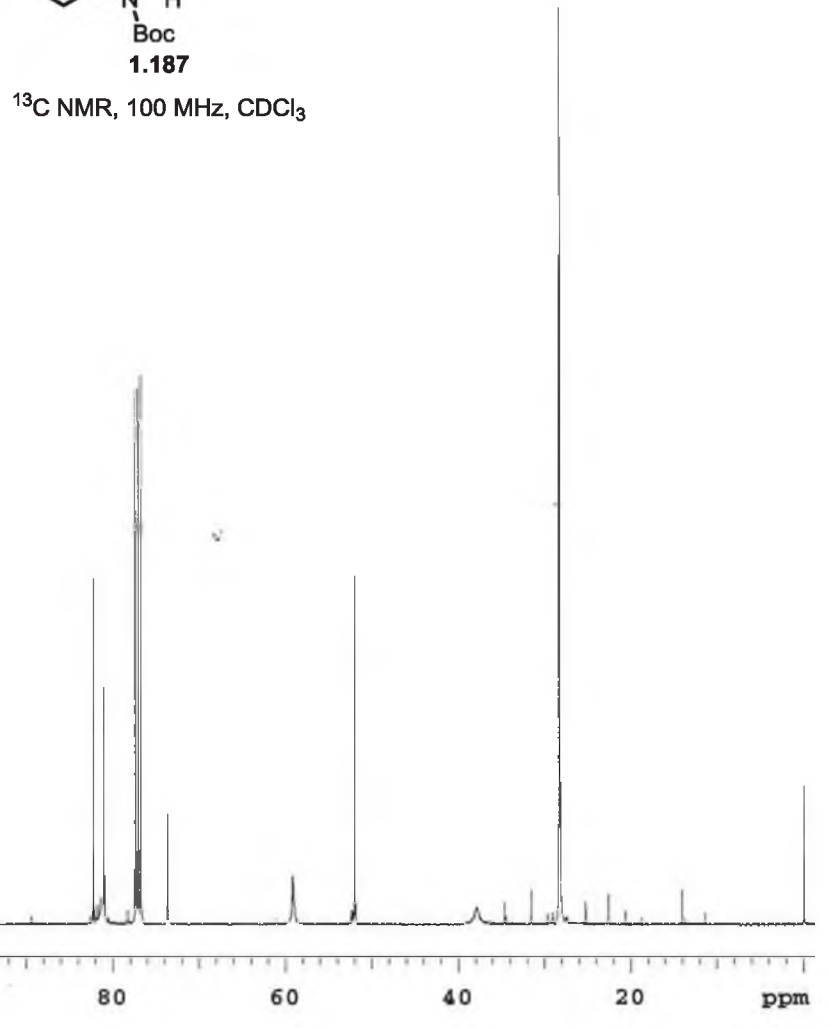


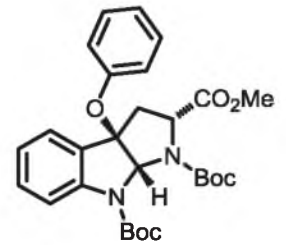

180
160
140
120
100



1.187

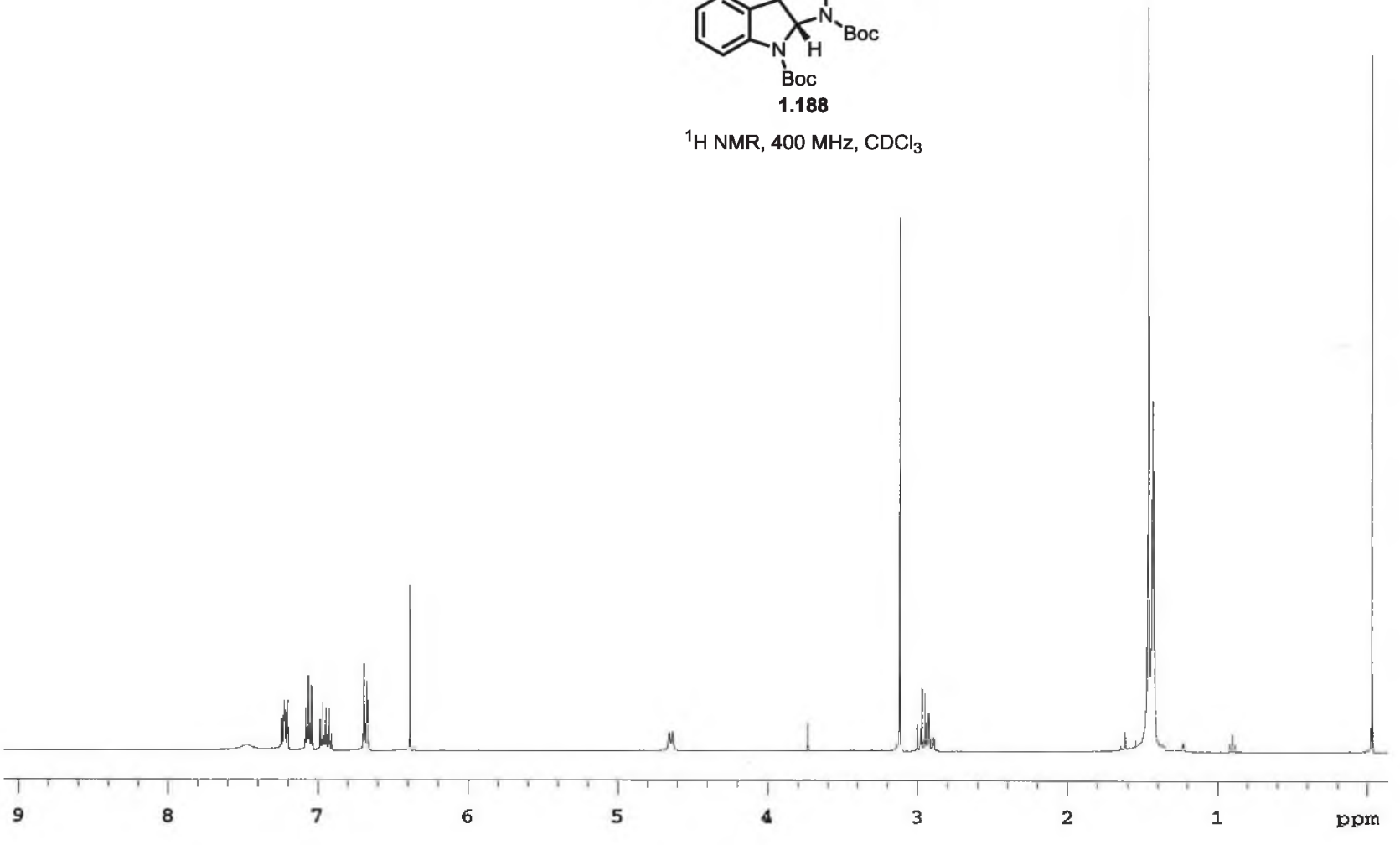
^{13}C NMR, 100 MHz, $CDCl_3$



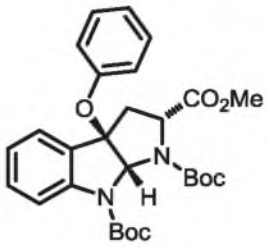


1.188

^{1}H NMR, 400 MHz, $CDCl_3$

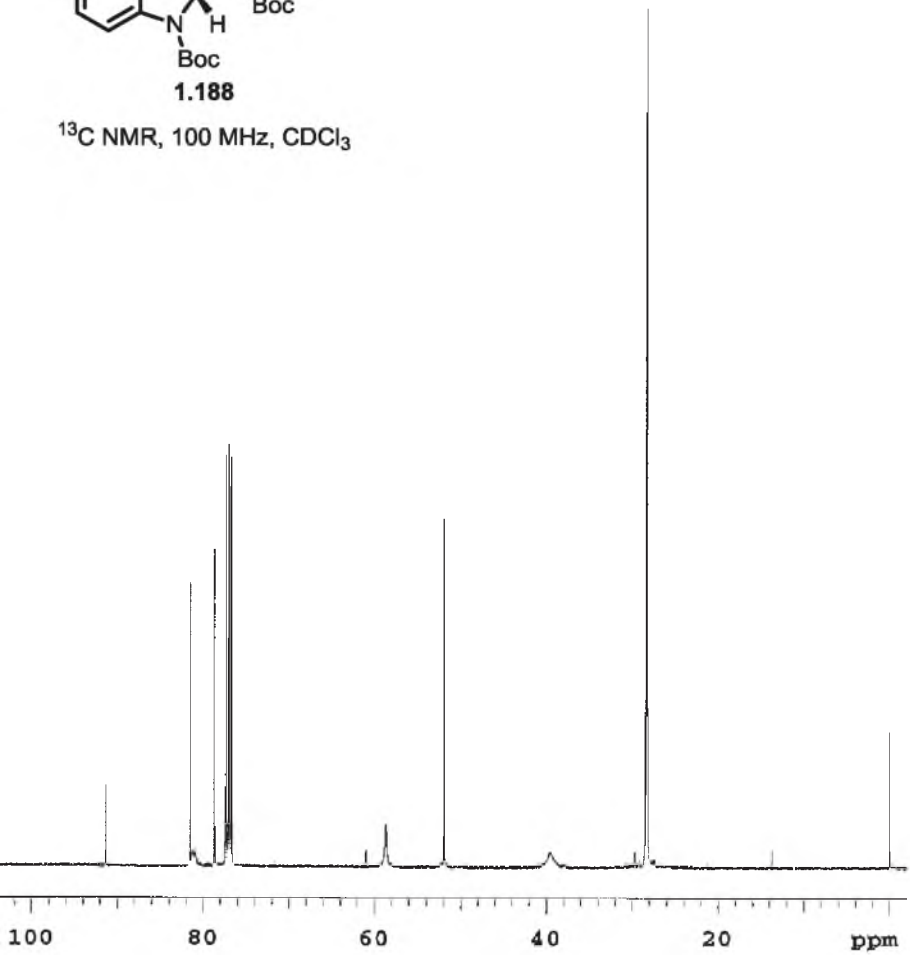


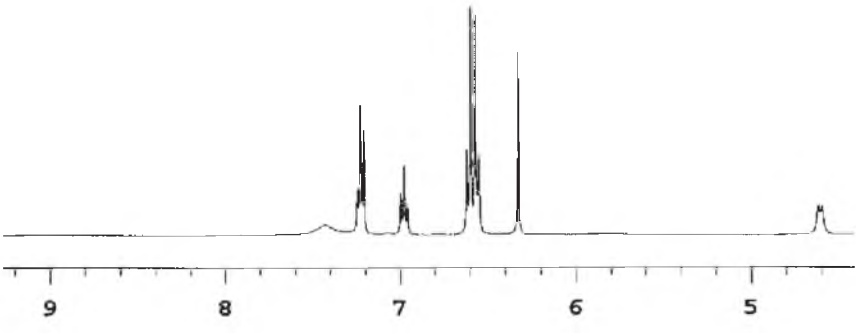

180
160
140
120



1.188

^{13}C NMR, 100 MHz, $CDCl_3$




9
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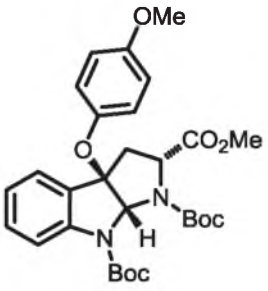
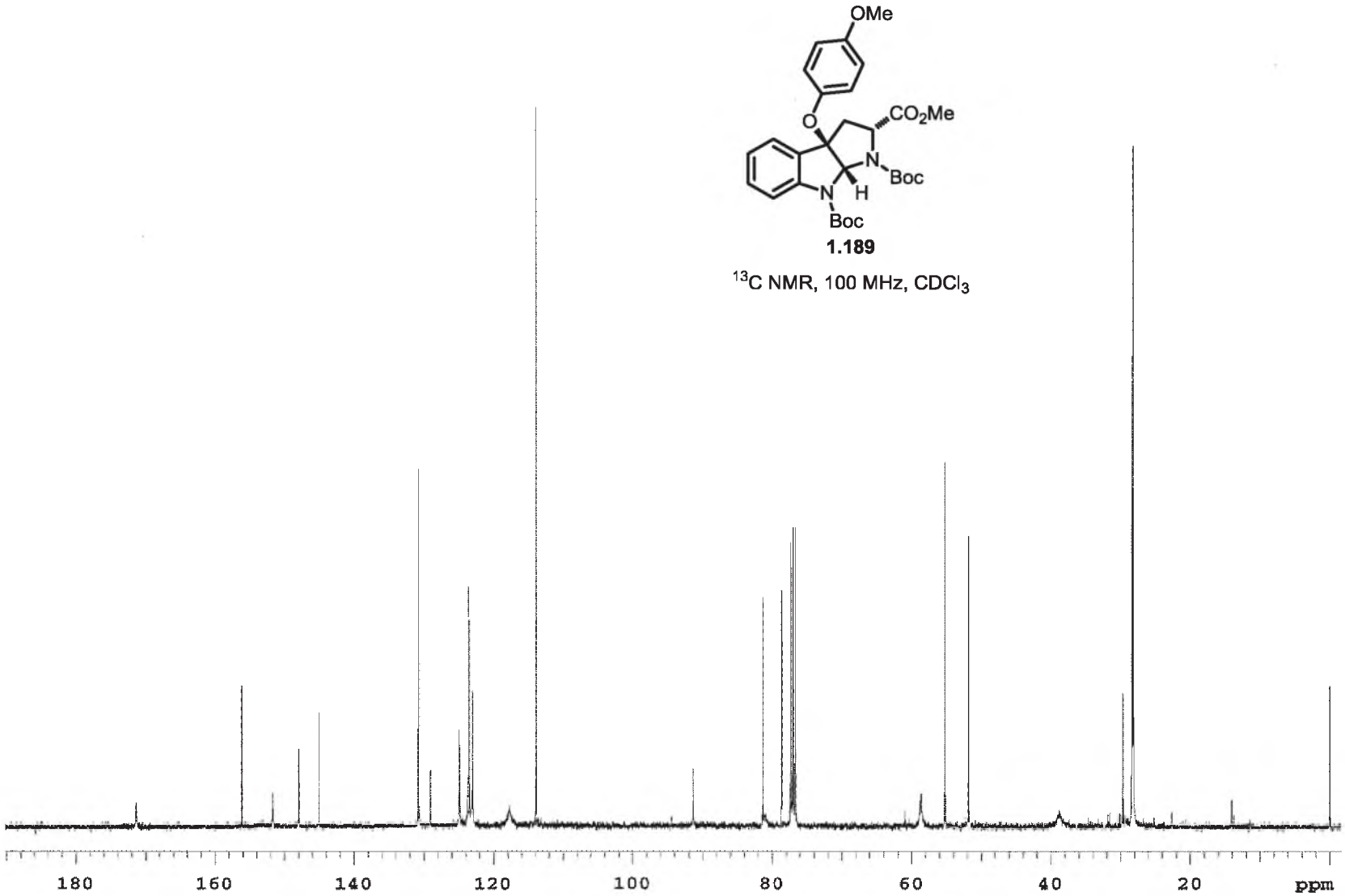


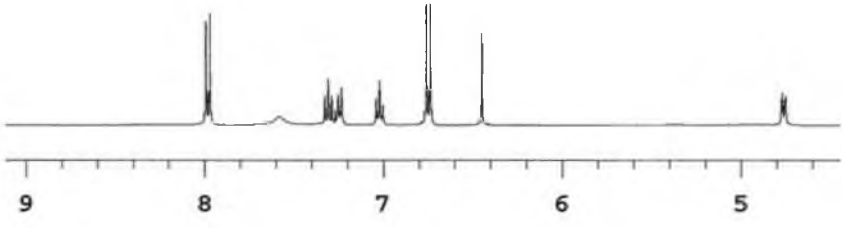
1.189

^{1}H NMR, 400 MHz, $CDCl_3$



1.189

^{13}C NMR, 100 MHz, $CDCl_3$


9
8
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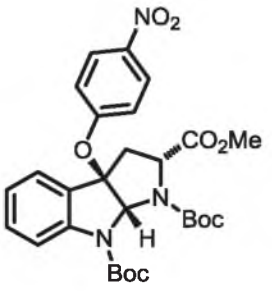
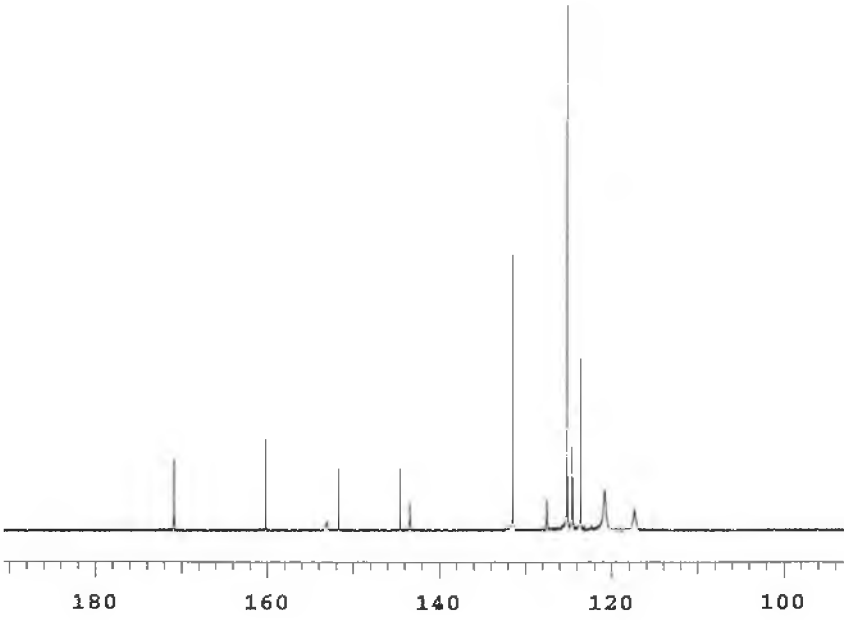
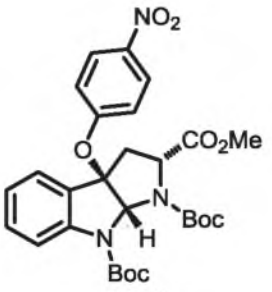


1.190

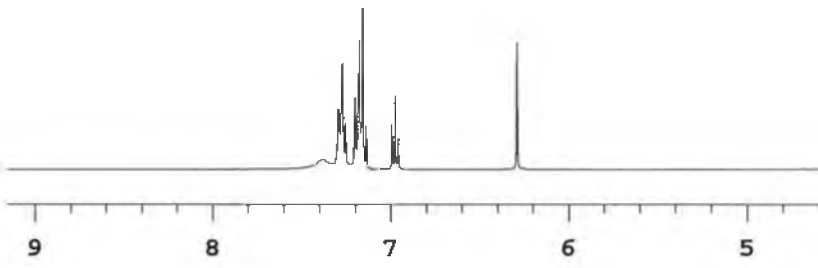
^{1}H NMR, 400 MHz, $CDCl_3$


180
160
140
120
100



1.190

^{13}C NMR, 100 MHz, $CDCl_3$


9
8
7
6
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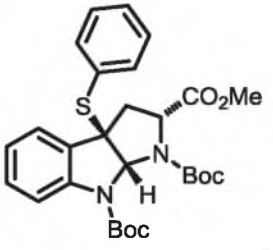
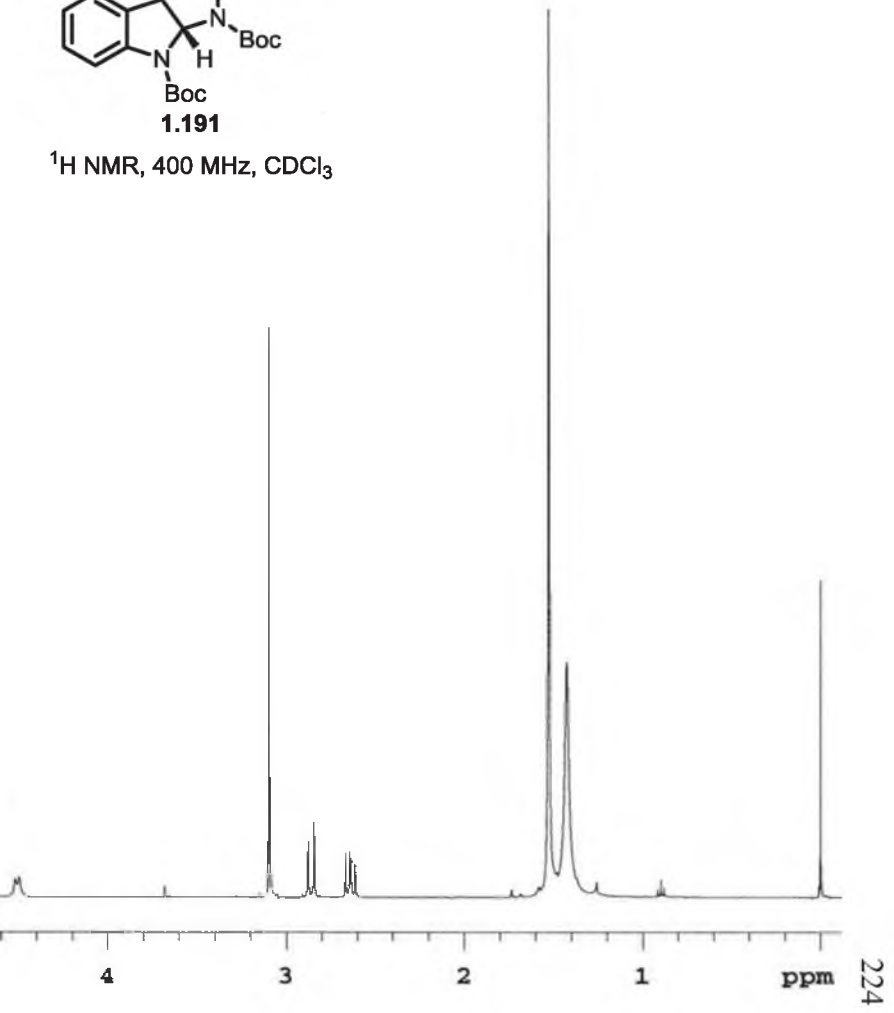
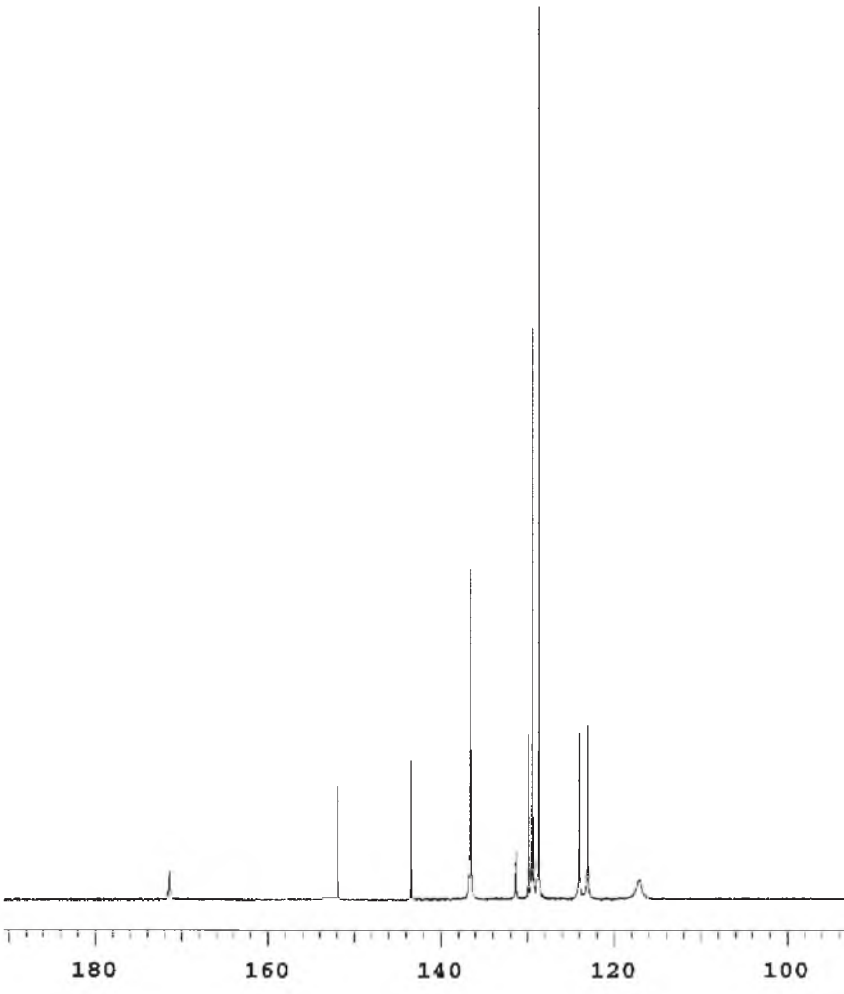
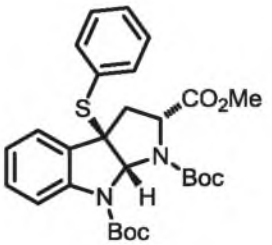


1.191

^{1}H NMR, 400 MHz, $CDCl_3$

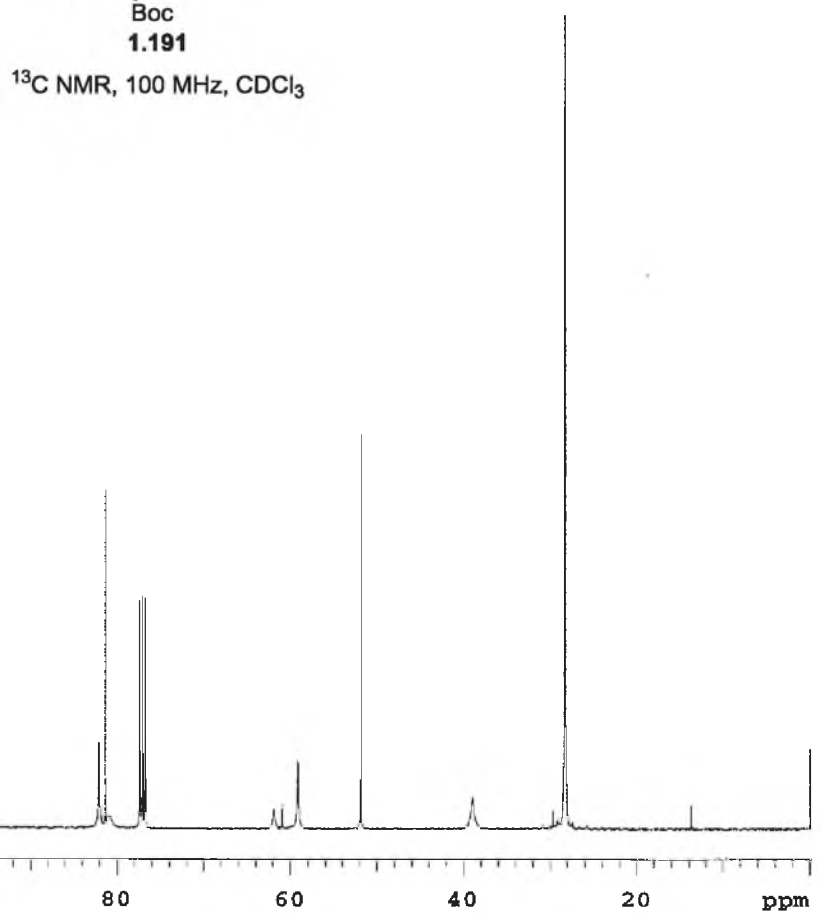


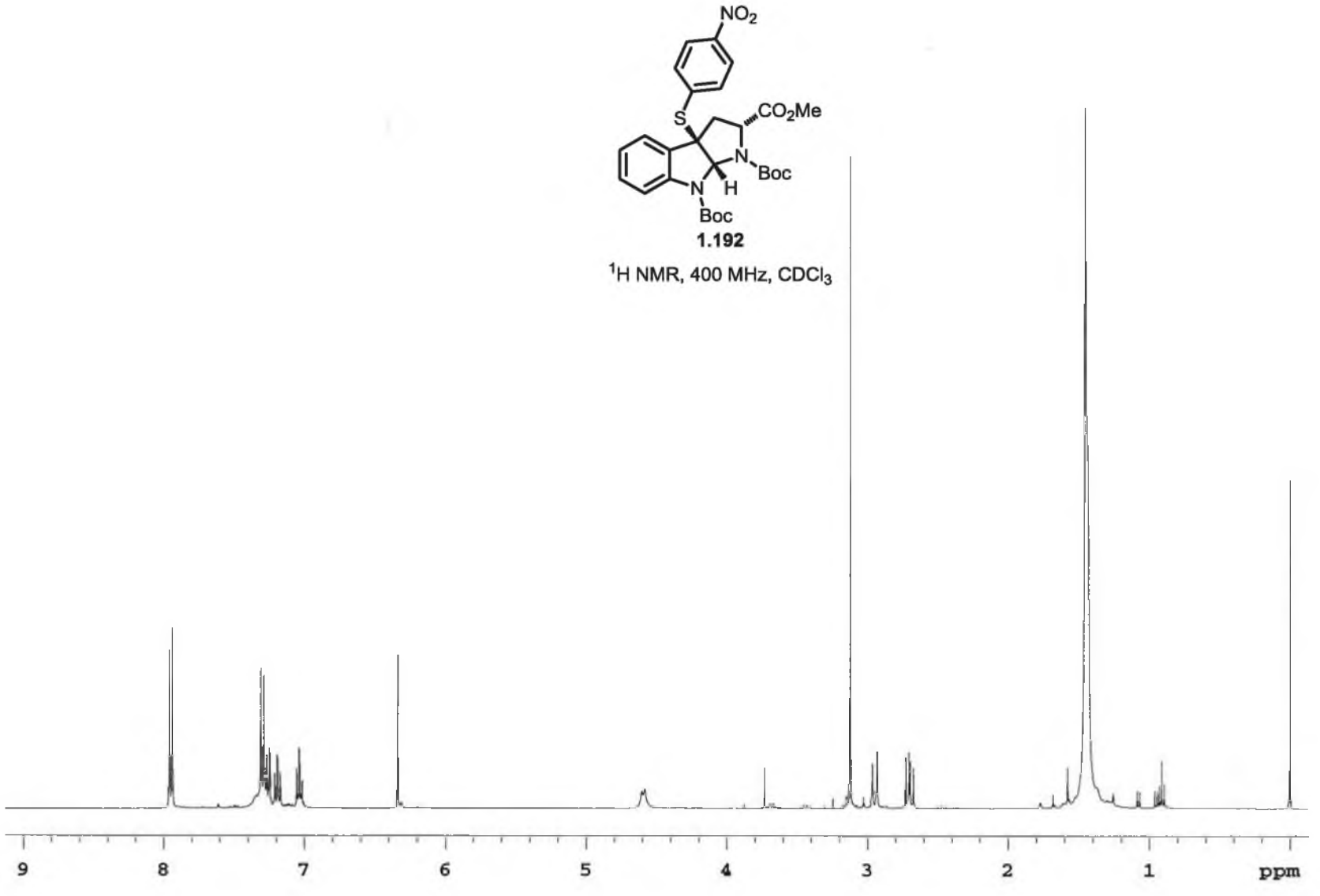

180
160
140
120
100

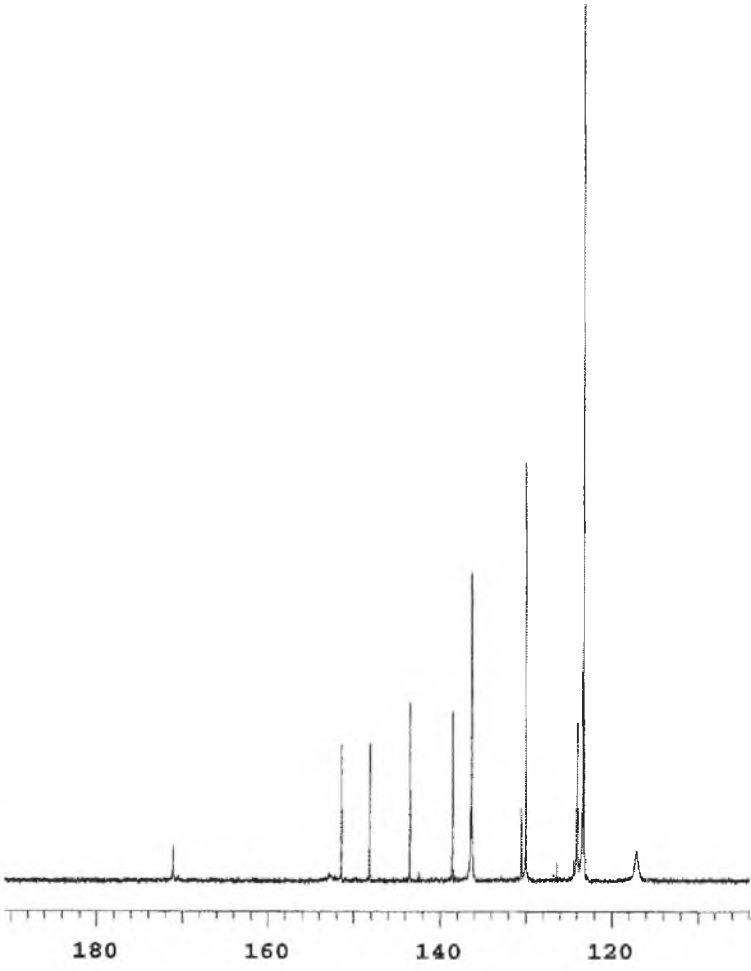


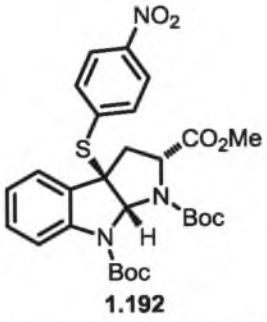
1.191

^{13}C NMR, 100 MHz, $CDCl_3$



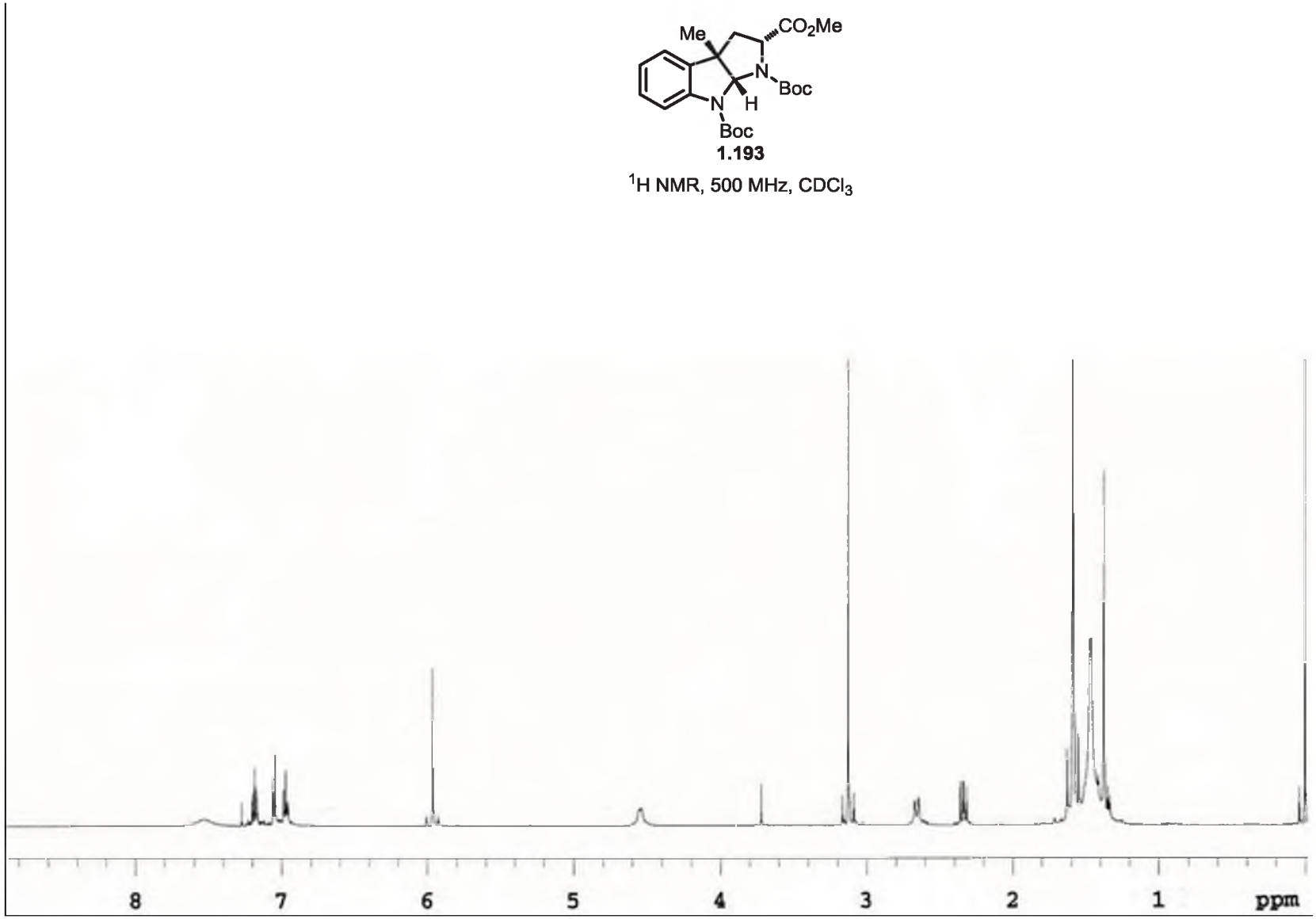

NO2
CO2Me
S
N
Boc
N
H
Boc
1.192
1H NMR, 400 MHz, CDCl3
9
8
7
6
5
4
3
2
1
ppm


180
160
140
120



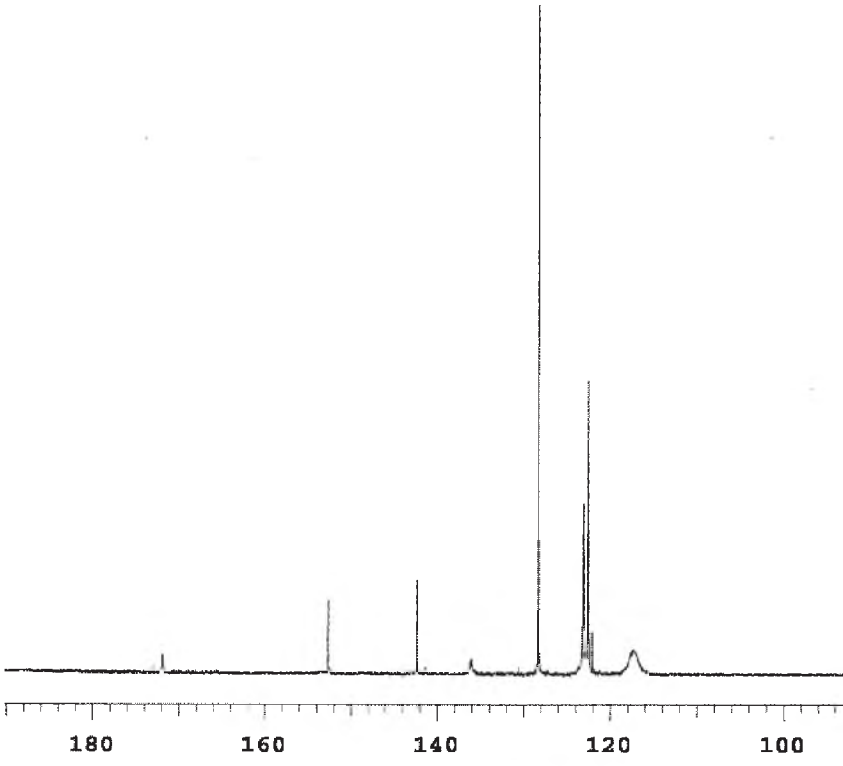
1.192

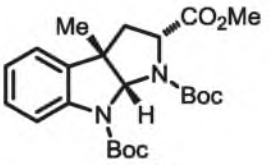
^{13}C NMR, 100 MHz, $CDCl_3$



1.193

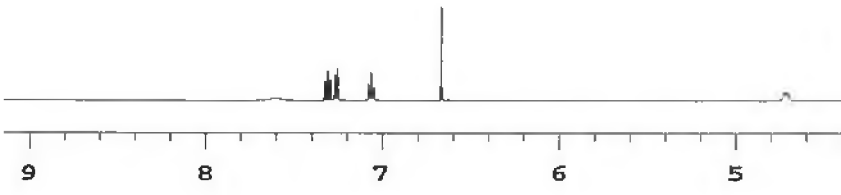
^{1}H NMR, 500 MHz, $CDCl_3$

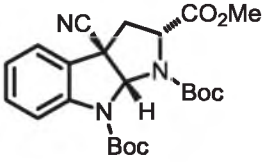

180
160
140
120
100



1.193

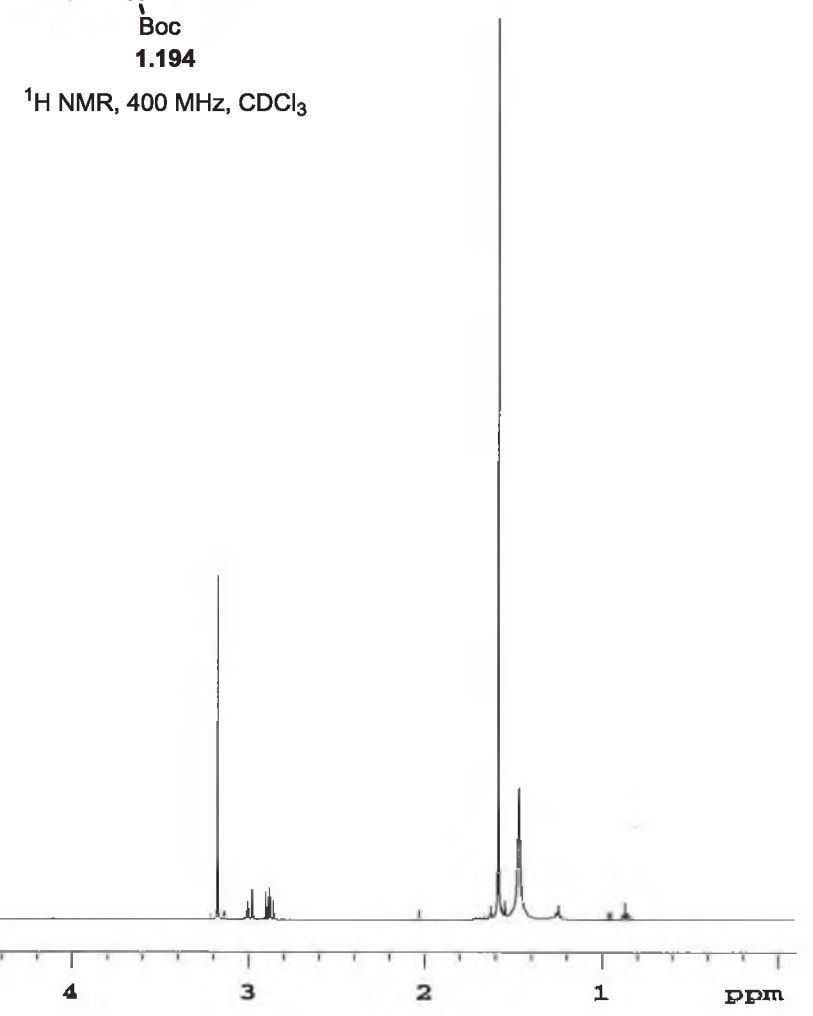
^{13}C NMR, 125 MHz, $CDCl_3$


9
8
7
6
5

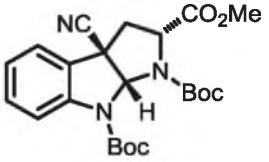


1.194

^{1}H NMR, 400 MHz, $CDCl_3$

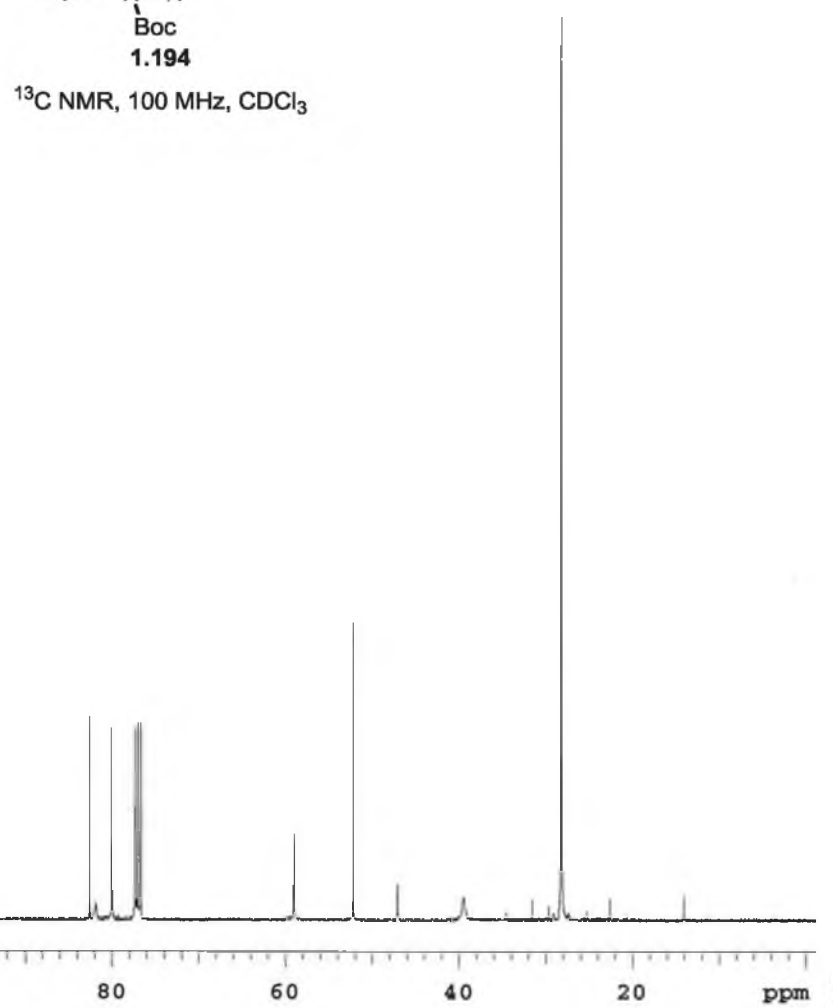


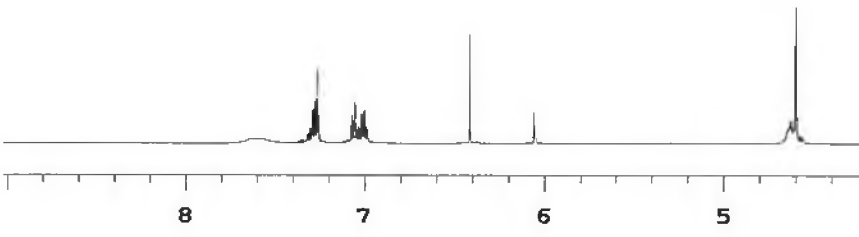

180
160
140
120
100

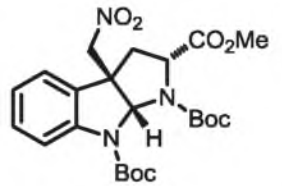


1.194

^{13}C NMR, 100 MHz, $CDCl_3$

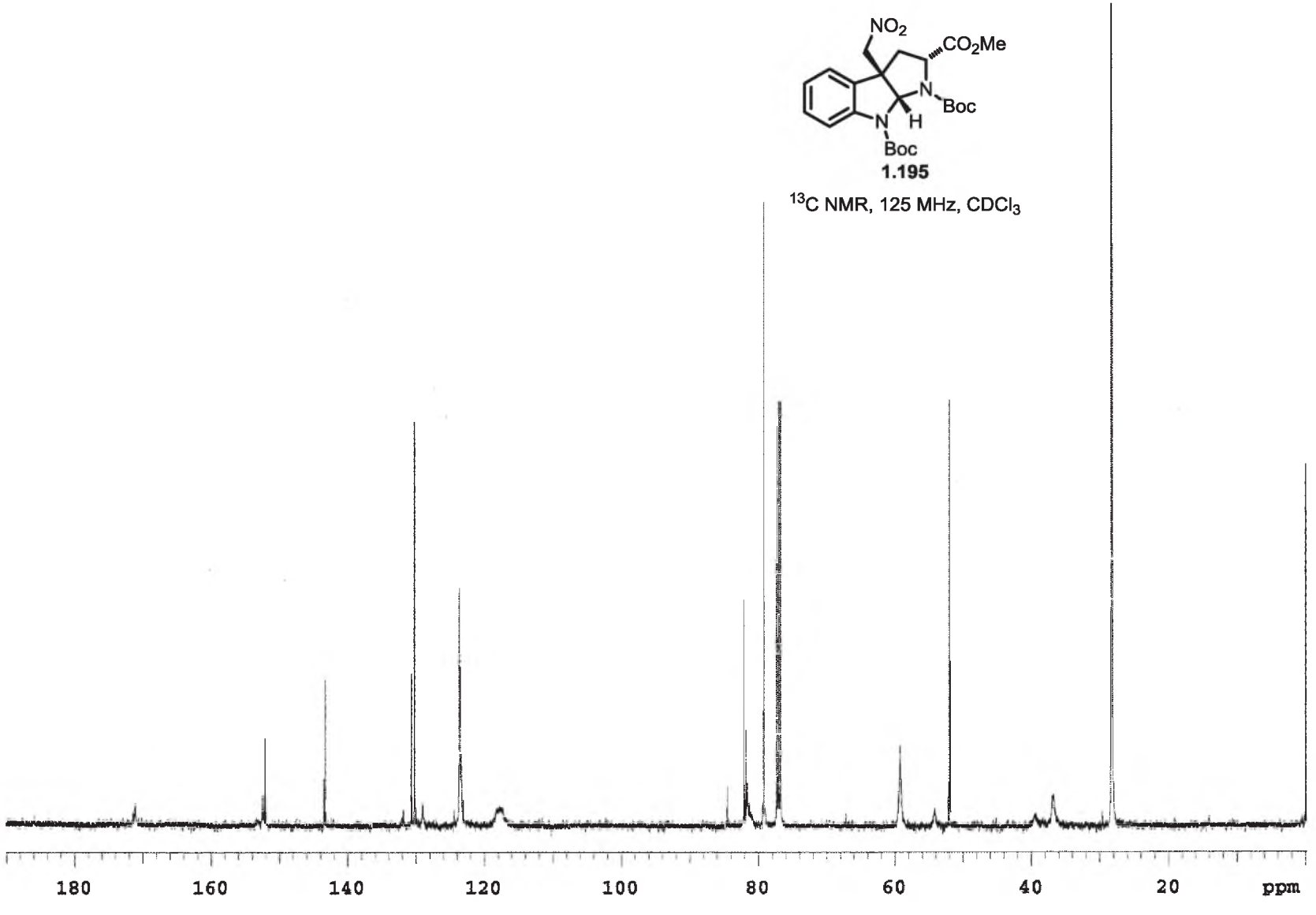


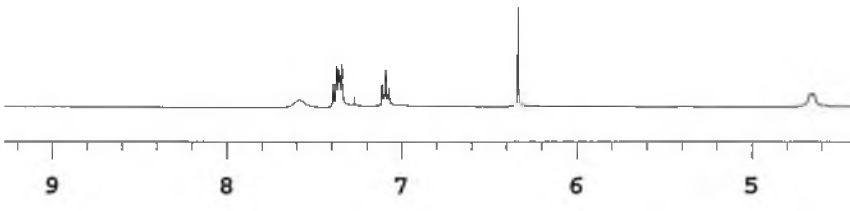

8
7
6
5

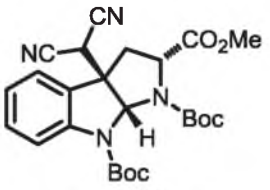


1.195

^{1}H NMR, 500 MHz, $CDCl_3$

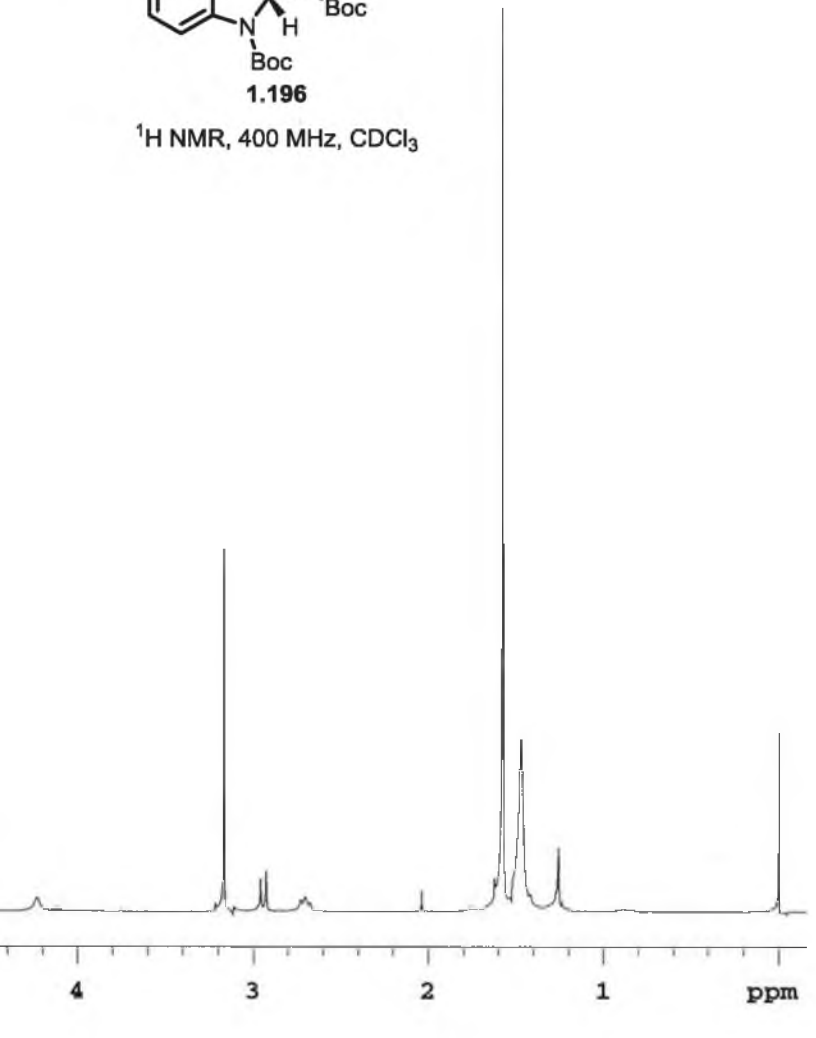

NO2
CO2Me
N
Boc
N
H
Boc
1.195
13C NMR, 125 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm

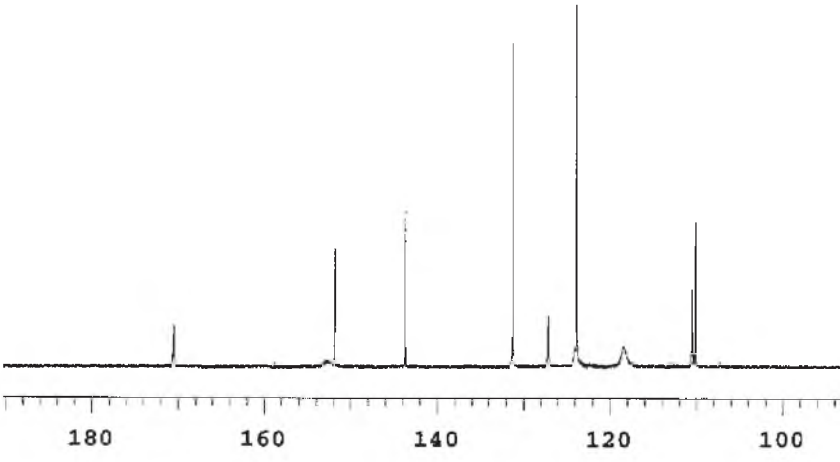

9
8
7
6
5

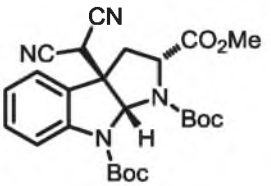


1.196

^{1}H NMR, 400 MHz, $CDCl_3$

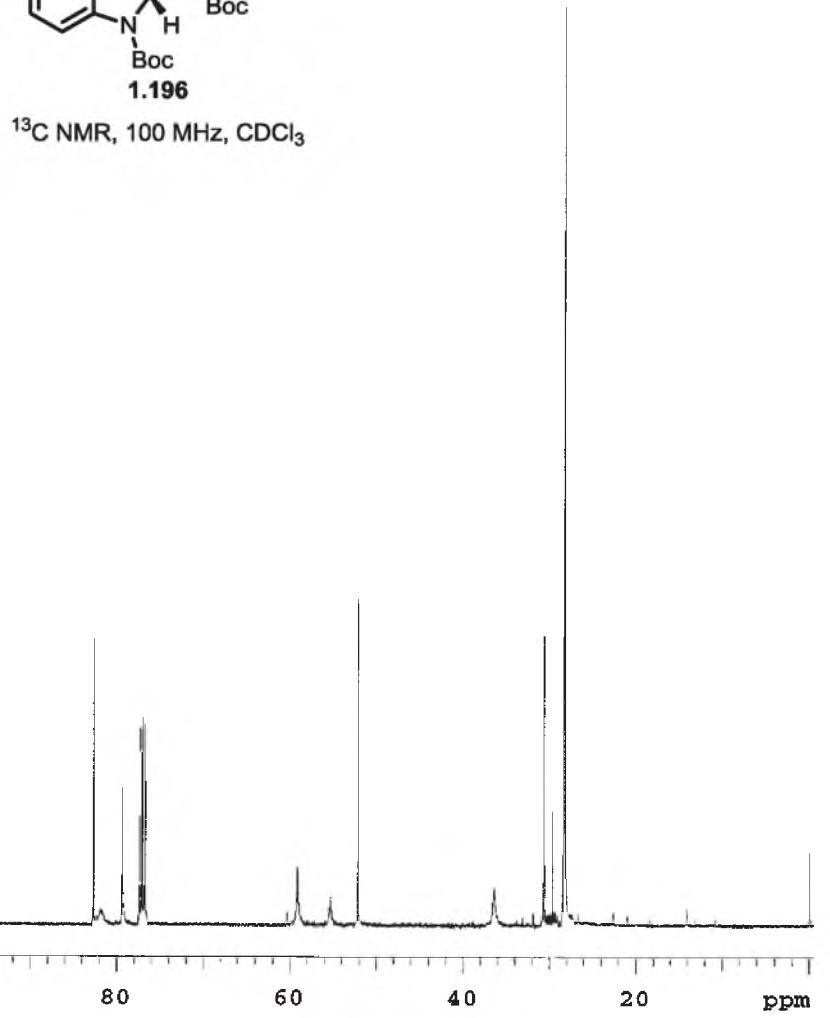


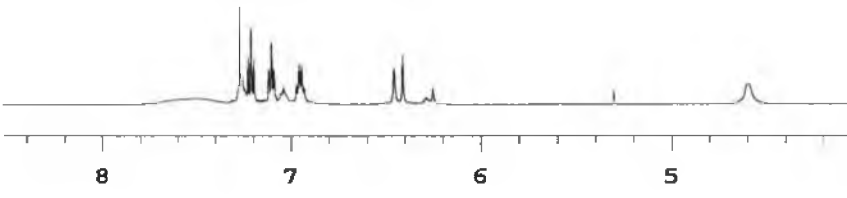

180
160
140
120
100

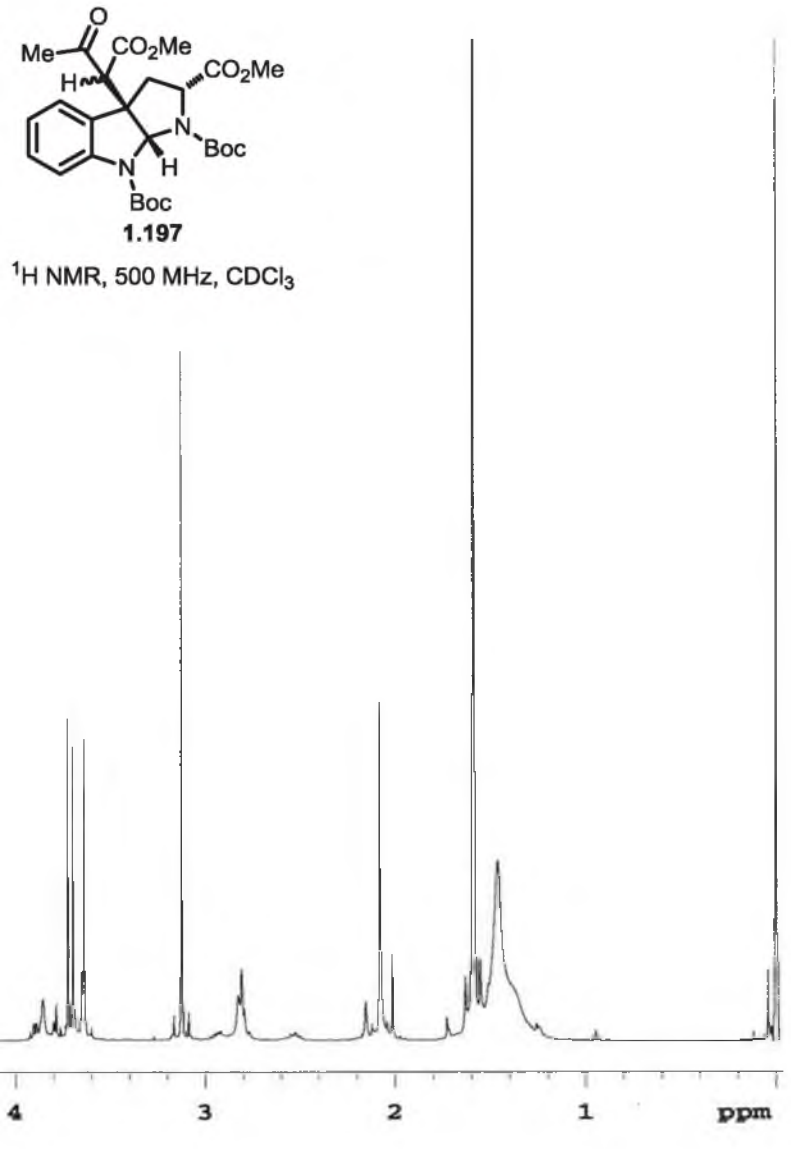


1.196

^{13}C NMR, 100 MHz, $CDCl_3$

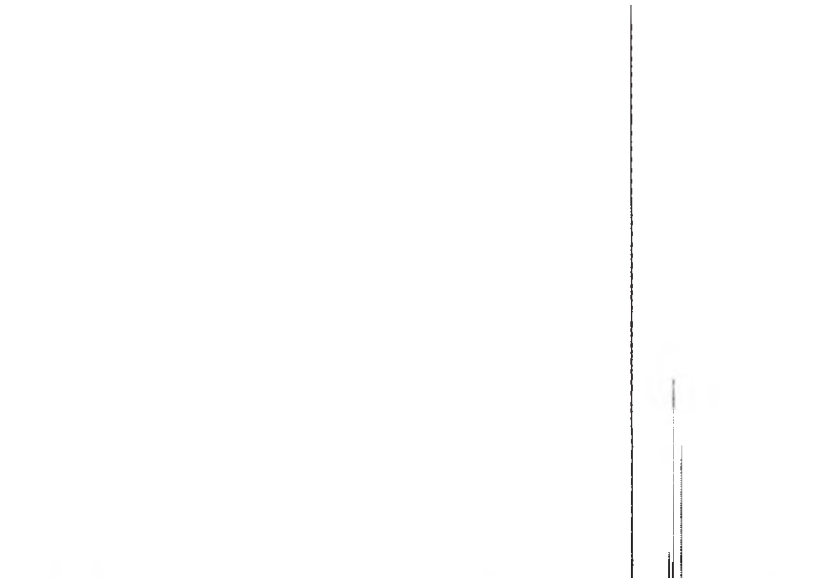



8
7
6
5



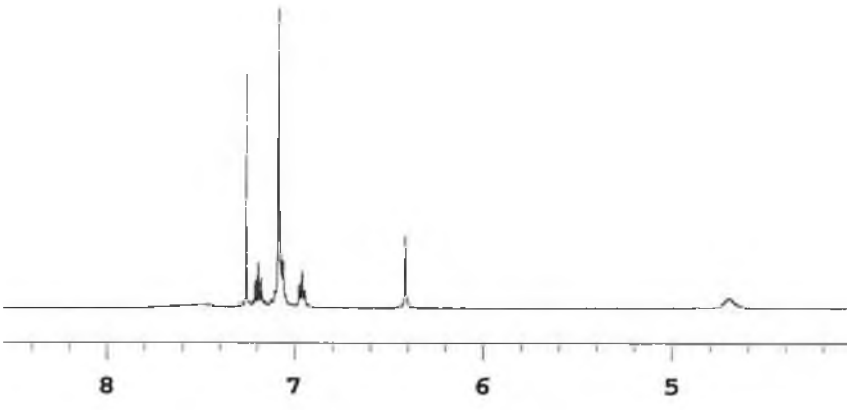
1.197

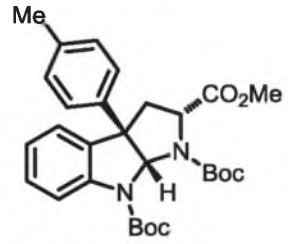
^{1}H NMR, 500 MHz, $CDCl_3$


200
180
160
140
120

1.197

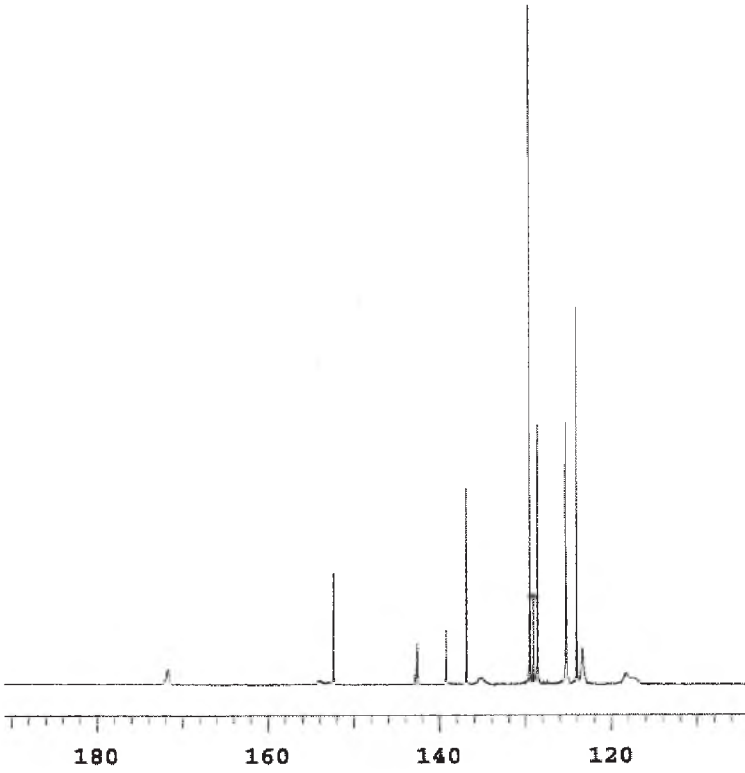
^{13}C NMR, 125 MHz, $CDCl_3$

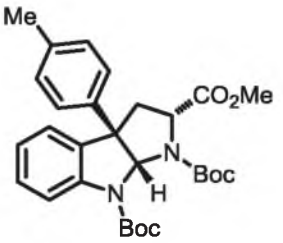

8
7
6
5



1.198

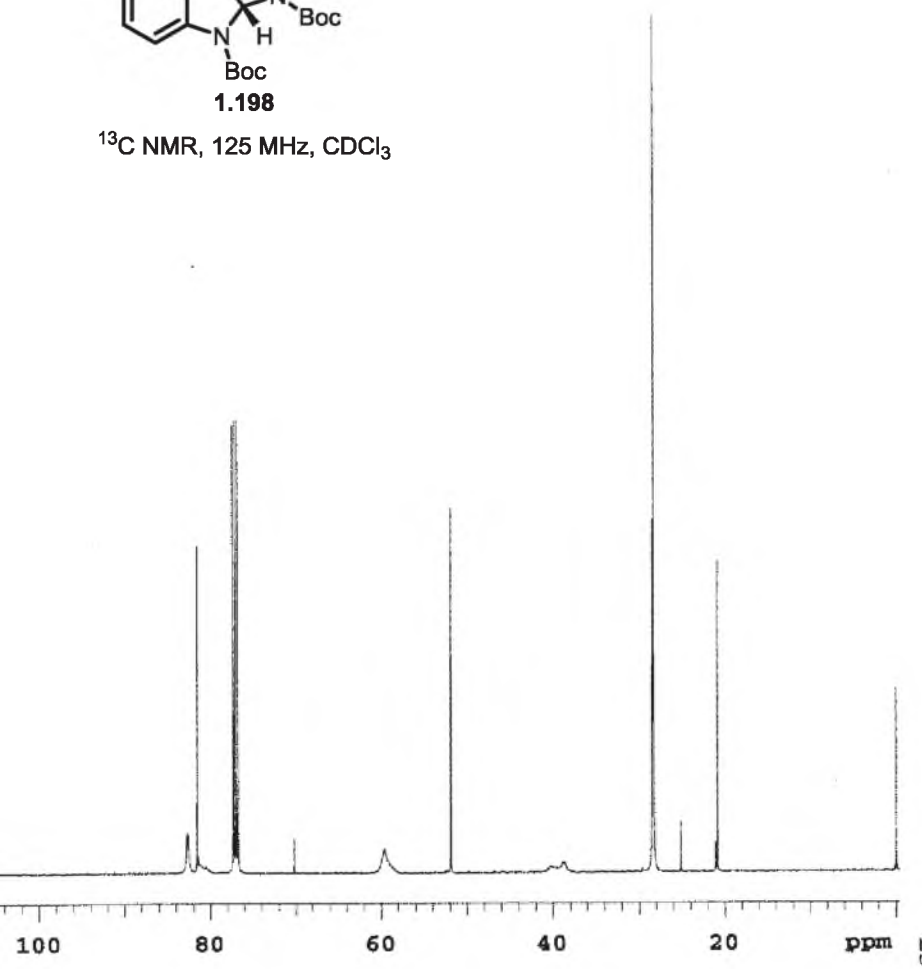
^{1}H NMR, 500 MHz, $CDCl_3$

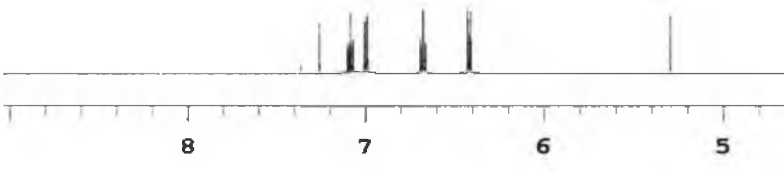

180
160
140
120

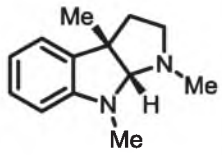


1.198

^{13}C NMR, 125 MHz, $CDCl_3$

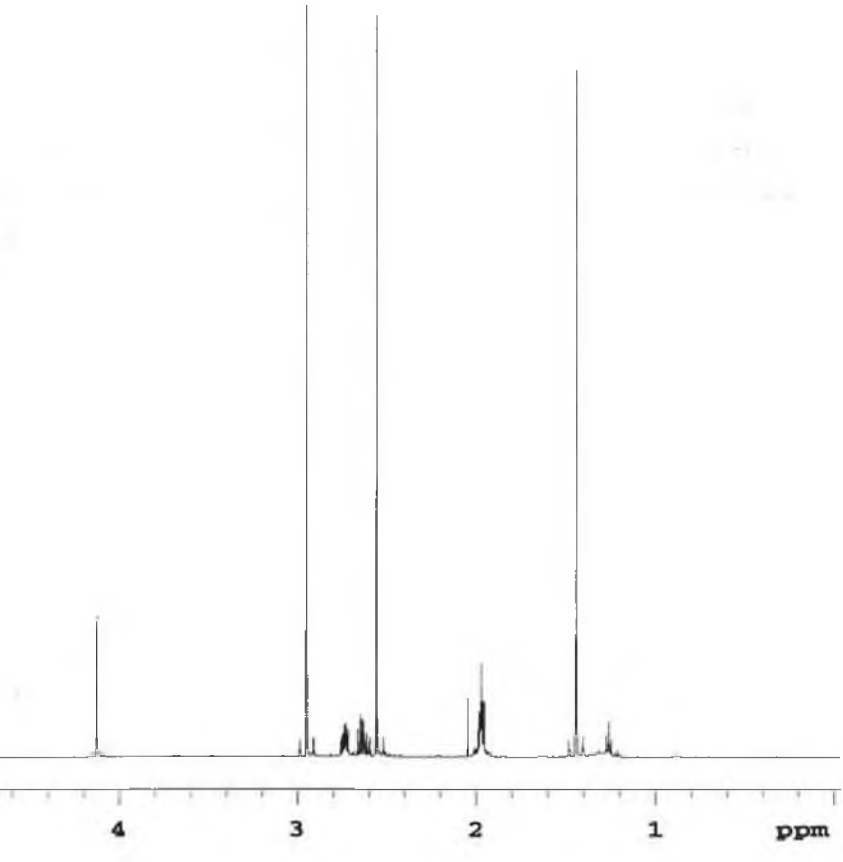


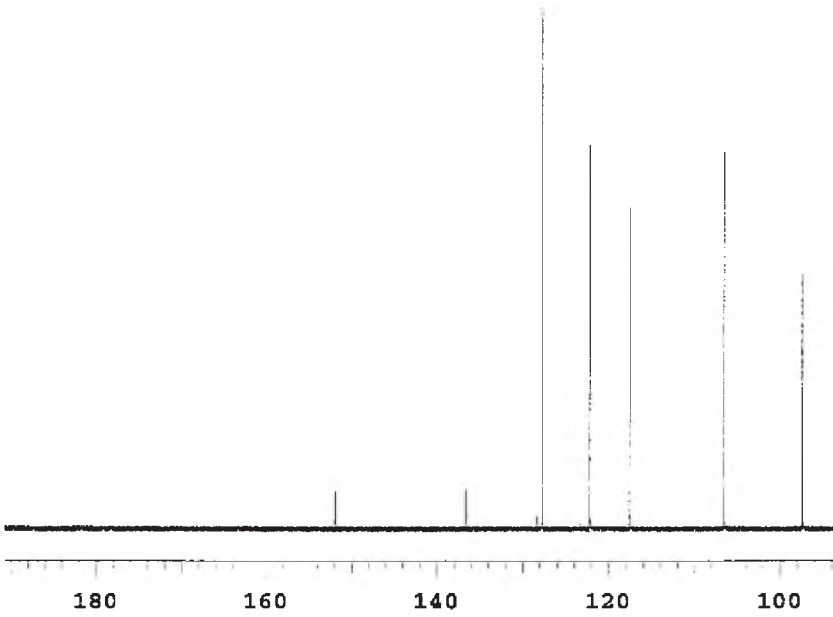

8
7
6
5

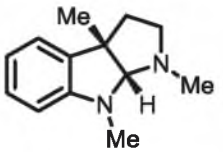


(-)-desoxyeseroline (**1.200**)

^{1}H NMR, 500 MHz, $CDCl_3$

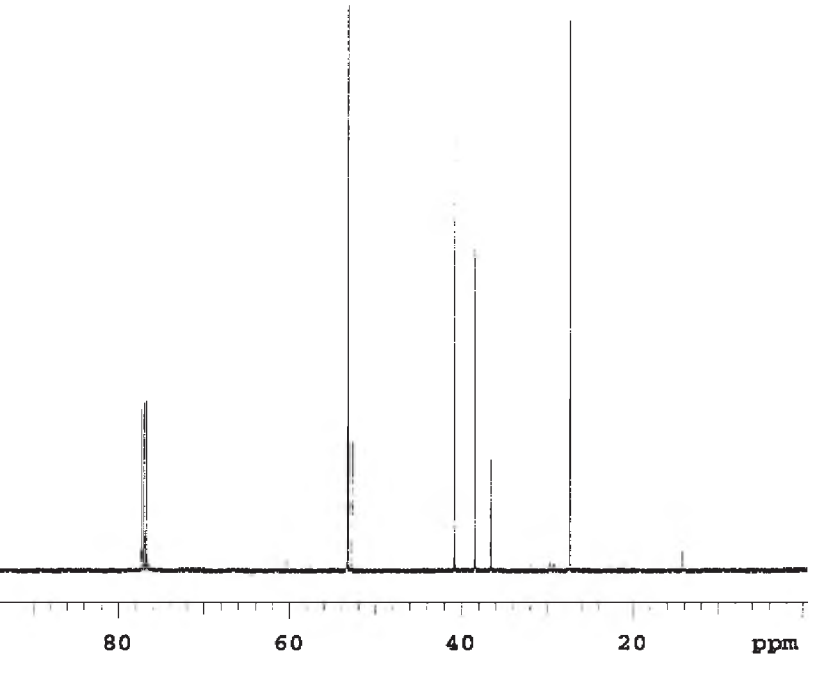



180
160
140
120
100



(-)-desoxyeseroline (**1.200**)

^{13}C NMR, 125 MHz, $CDCl_3$

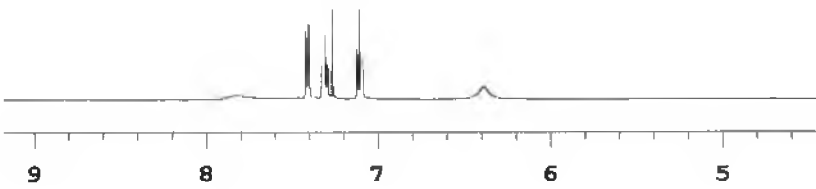


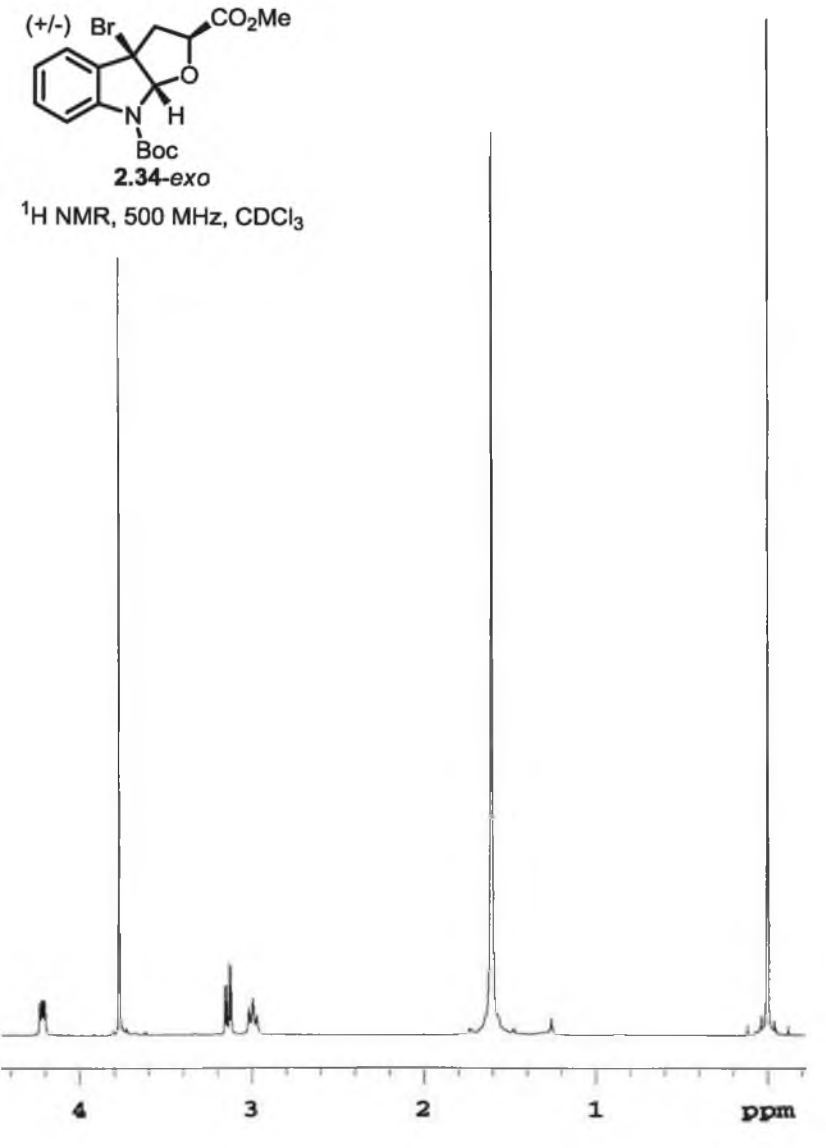
Desoxyeseroline (1.200) - ^{1}H NMR ($CDCl_3$)		
Synthetic (this work) (500 MHz) ppm, multiplicity, *J* (Hz)	Synthetic (Kulkarni, 2009) (300 MHz) ppm, multiplicity, *J* (Hz)	Synthetic (Nakagawa, 2000) (400 MHz) ppm, multiplicity, *J* (Hz)
7.08, t, 7.8	7.00, t, 7.6	7.07, t, 7.6
6.99, d, 7.3	6.98, d, 7.8	6.98, d, 7.8
6.67, t, 7.3	6.68, t, 7.4	6.66, t, 7.4
6.42, d, 7.8	6.42, d, 7.8	6.40, d, 7.8
4.12, s	4.15, s	4.10, s
2.95, s	2.94, s	2.95, s
2.60-2.75, m	2.61-2.78, m	2.60-2.74, m
2.56, s	2.55, s	2.55, s
1.95-2.00, m	1.90-2.09, m	1.94-2.97, m
1.44, s	1.43, s	1.43, s

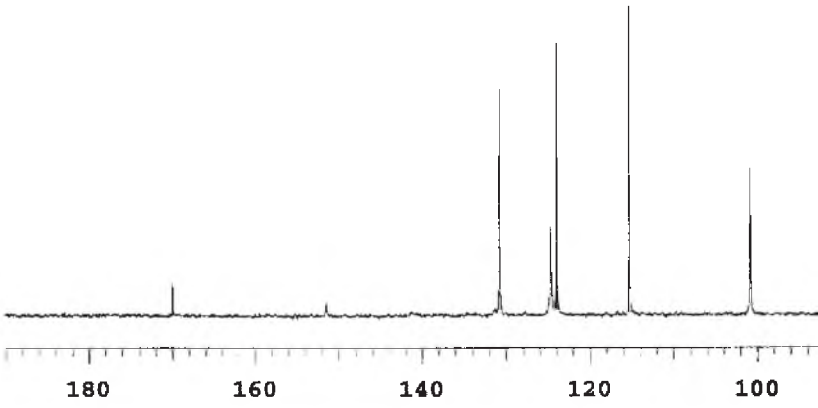
Desoxyeseroline (1.200) - ^{13}C NMR ($CDCl_3$)		
Synthetic (this work) (125 MHz) ppm	Synthetic (Kulkarni, 2009) (75 MHz) ppm	Synthetic (Nakagawa, 2000) (100 MHz) ppm
151.9	151.9	151.9
136.6	136.6	136.6
127.7	127.6	127.6
122.2	122.1	122.1
117.5	117.4	117.4
106.5	106.4	106.5
97.5	97.4	97.5
53.2	53.1	53.2
52.6	52.5	52.6
40.8	40.8	40.8
38.4	38.4	38.5
36.5	36.4	36.5
27.3	27.3	27.3

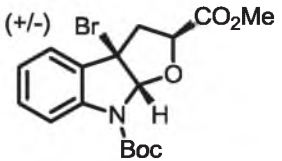
APPENDIX B

NMR SPECTRA, HPLC AND MS/MS DATA CHAPTER 2


9
8
7
6
5

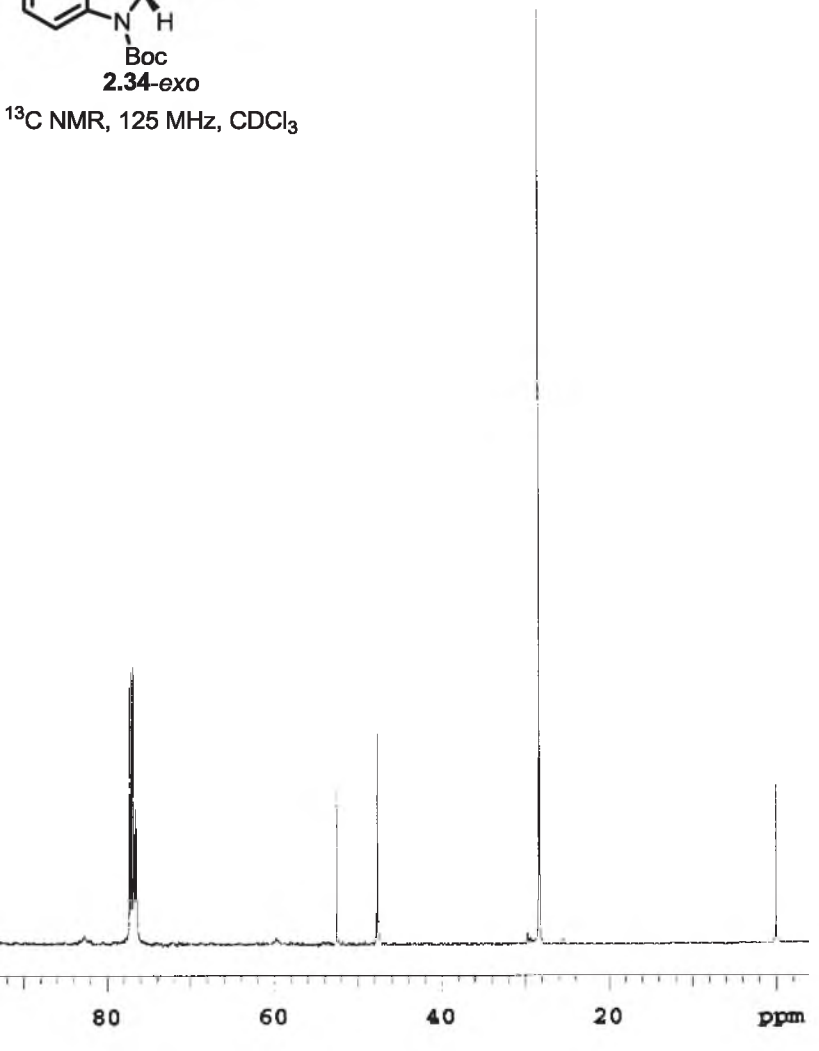

(+/-) Br
CO2Me
O
N
H
Boc
2.34-exo
1H NMR, 500 MHz, CDCl3
4
3
2
1
ppm

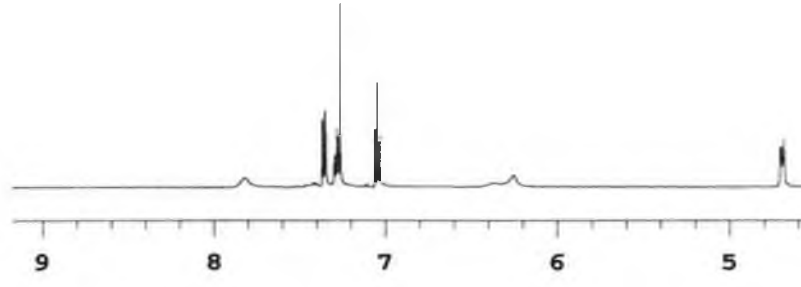

180
160
140
120
100

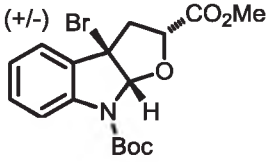


2.34-*exo*

^{13}C NMR, 125 MHz, $CDCl_3$

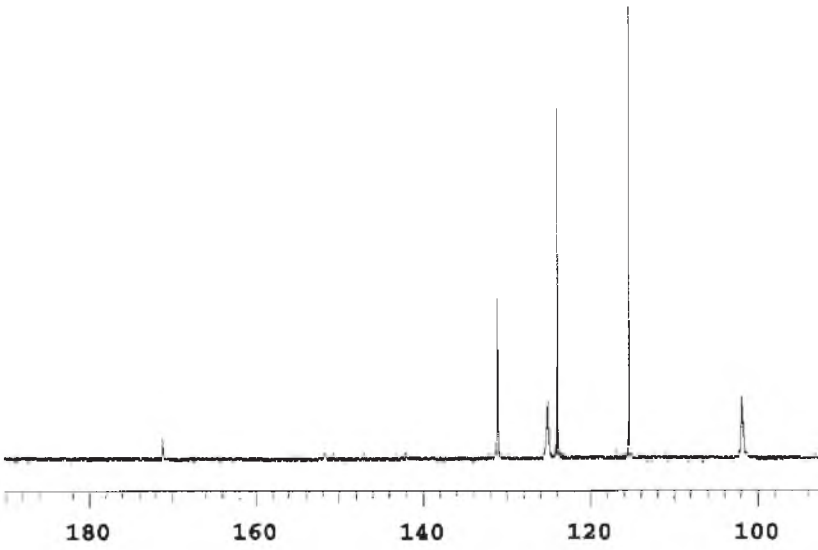


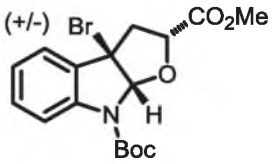

9
8
7
6
5



2.34-*endo*

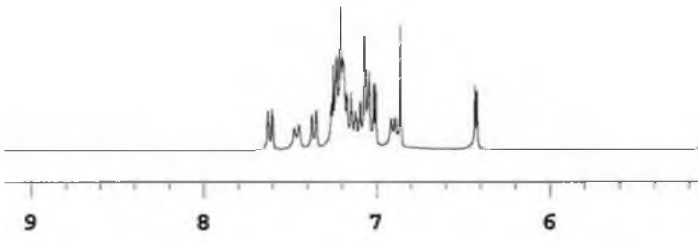
^{1}H NMR, 500 MHz, $CDCl_3$

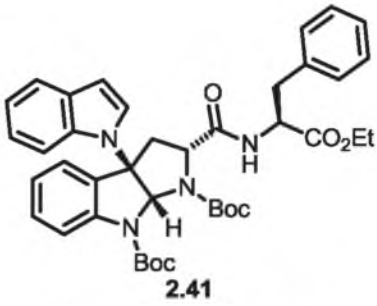

180
160
140
120
100



2.34-*endo*

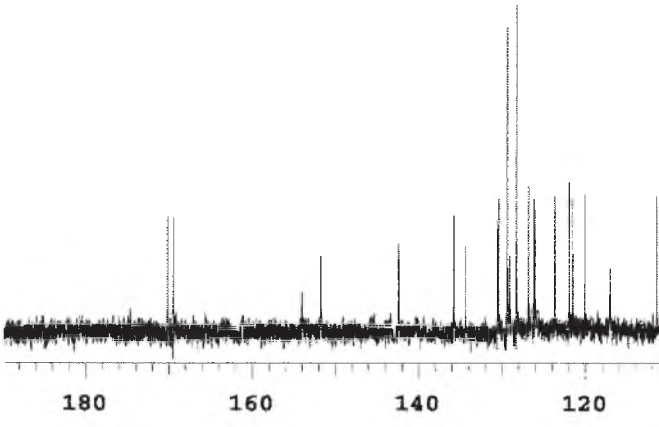
^{13}C NMR, 125 MHz, $CDCl_3$

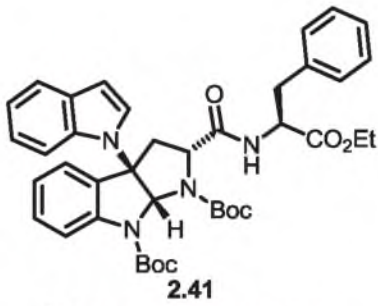

9
8
7
6



2.41

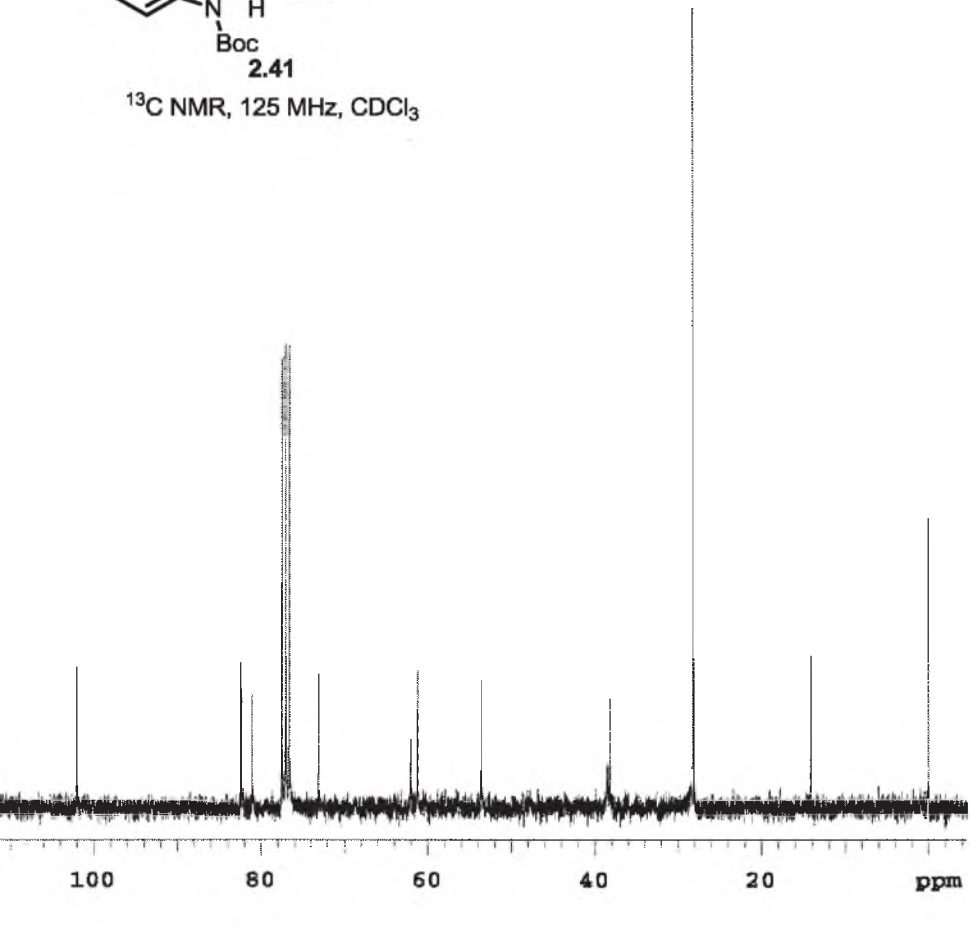
^{1}H NMR, 300 MHz, $CDCl_3$

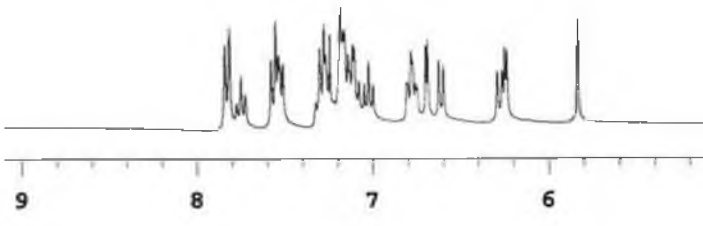

180
160
140
120

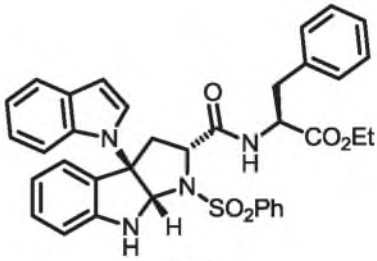


2.41

^{13}C NMR, 125 MHz, $CDCl_3$

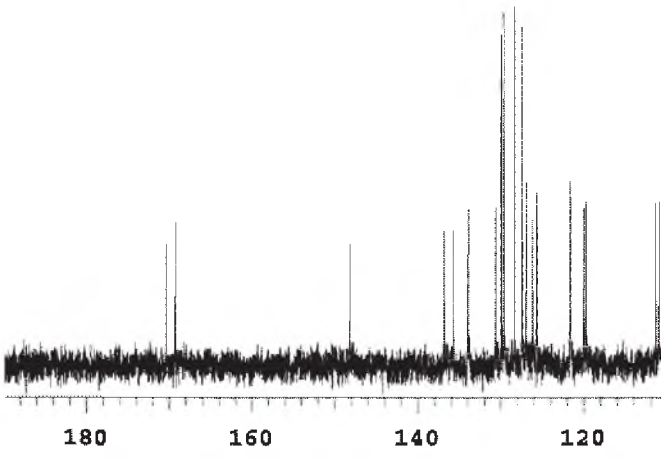


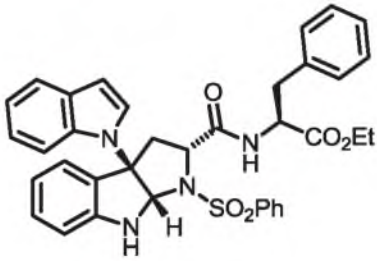

9
8
7
6



2.42

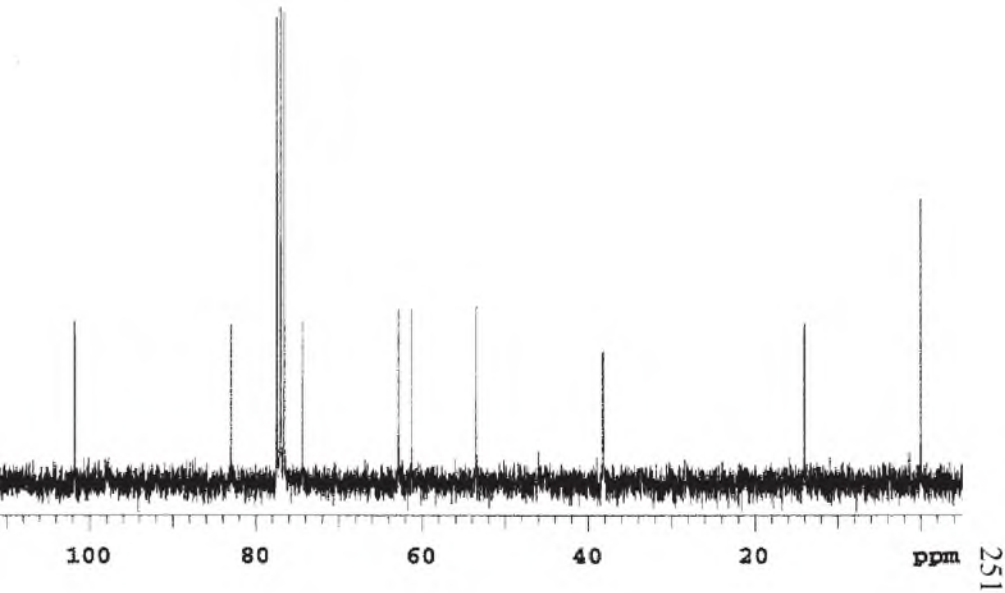
^{1}H NMR, 300 MHz, $CDCl_3$

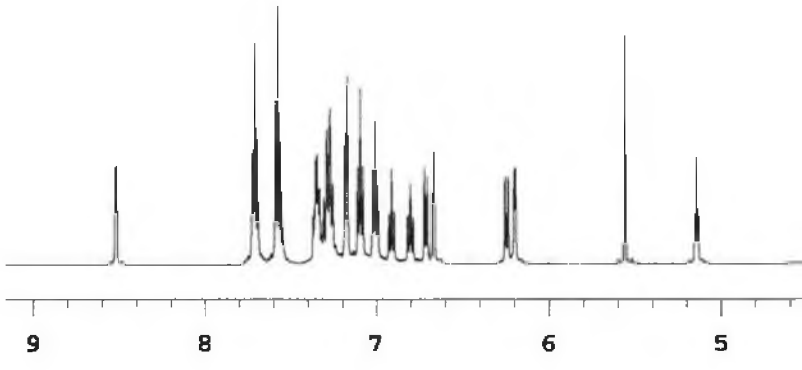

180
160
140
120



2.42

^{13}C NMR, 125 MHz, $CDCl_3$

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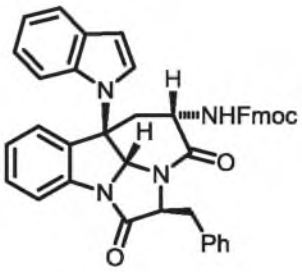
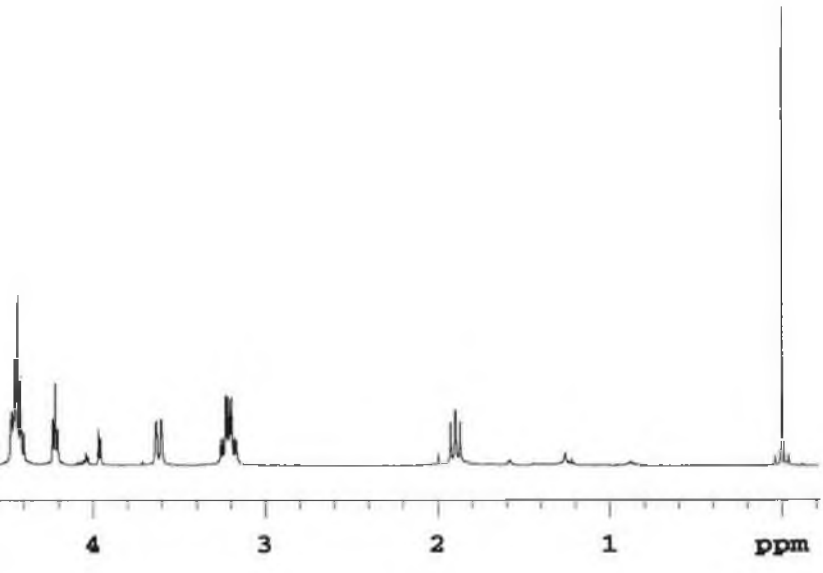
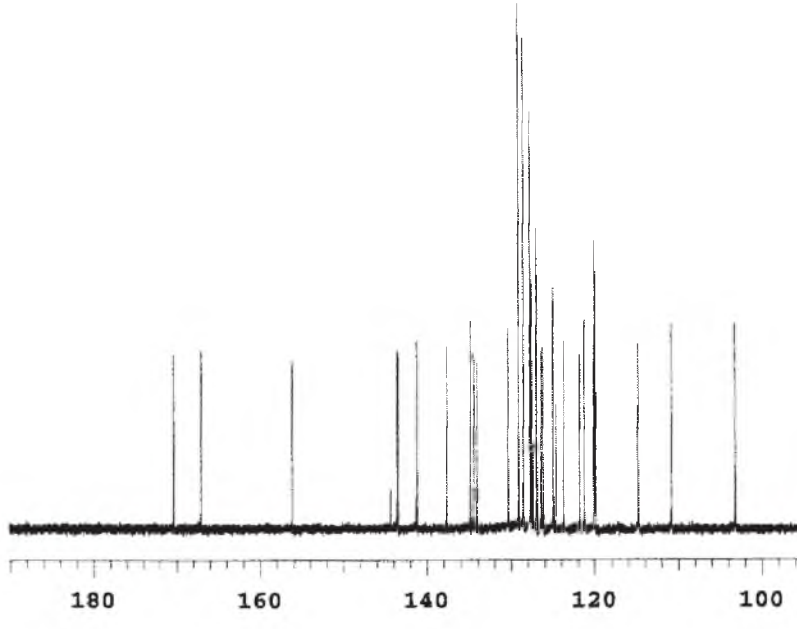


2.53

^{1}H NMR, 500 MHz, $CDCl_3$

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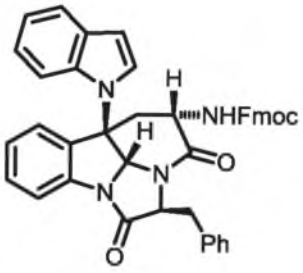
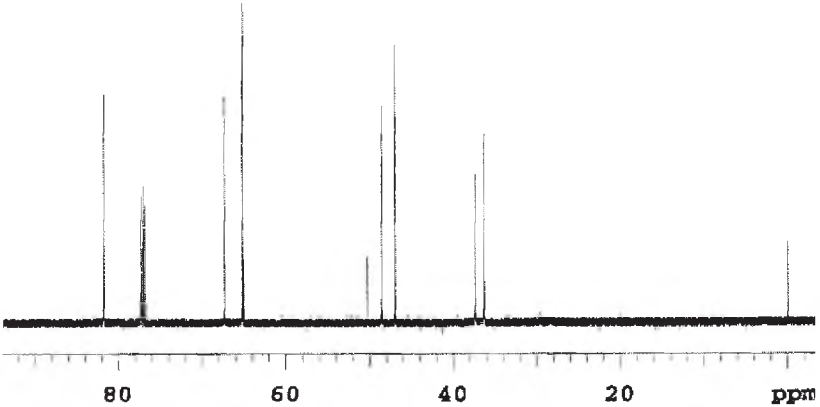
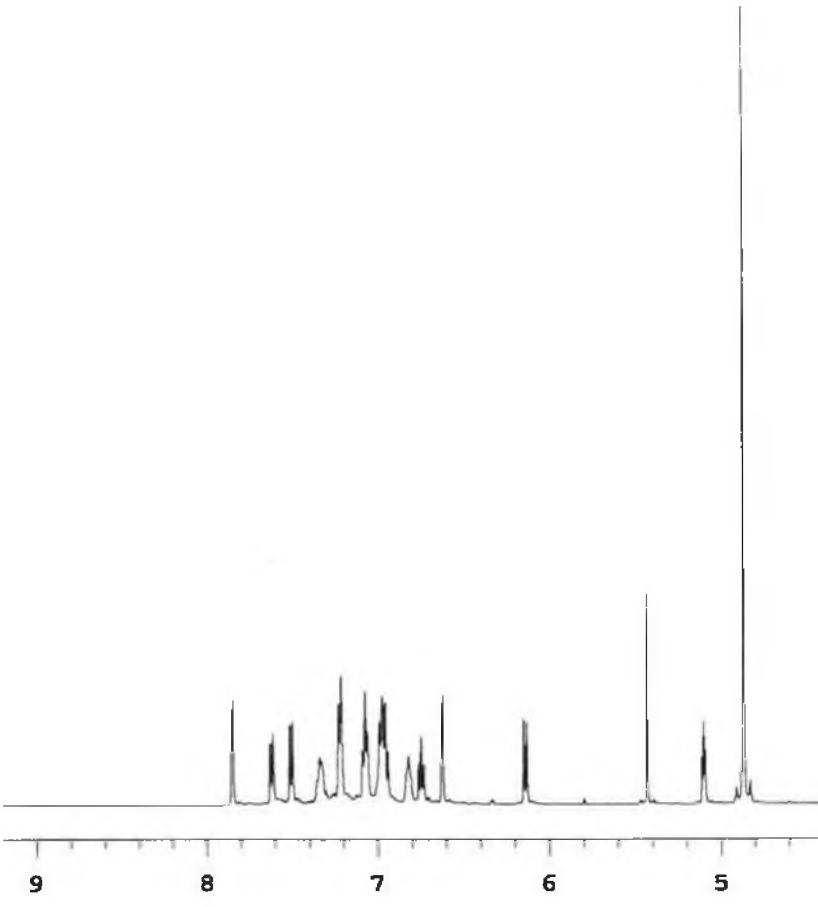


2.53

^{13}C NMR, 125 MHz, $CDCl_3$

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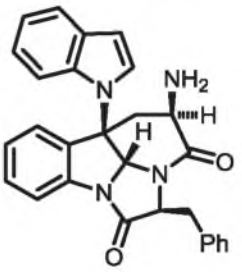
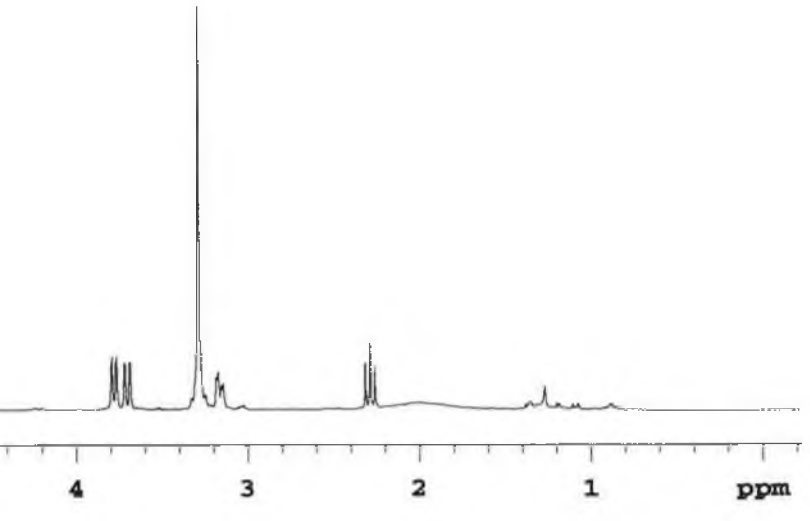
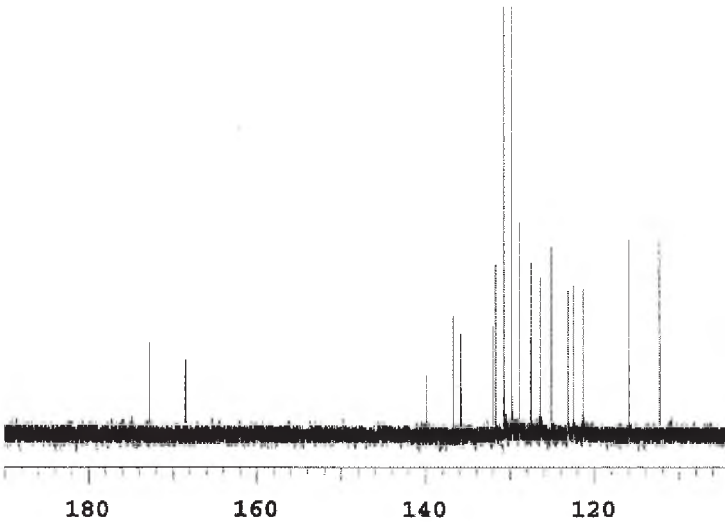


2.54

^{1}H NMR, 500 MHz, CD_3OD

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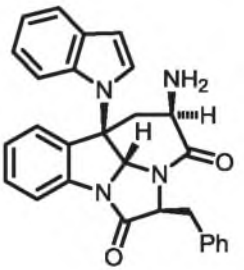
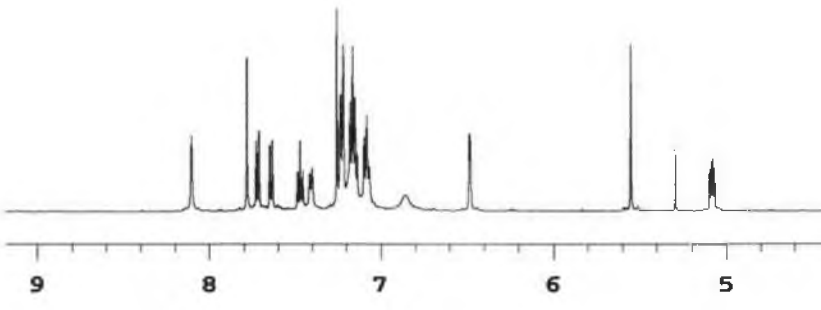


2.54

^{13}C NMR, 125 MHz, CD_3OD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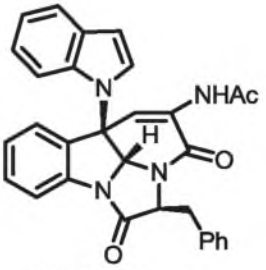
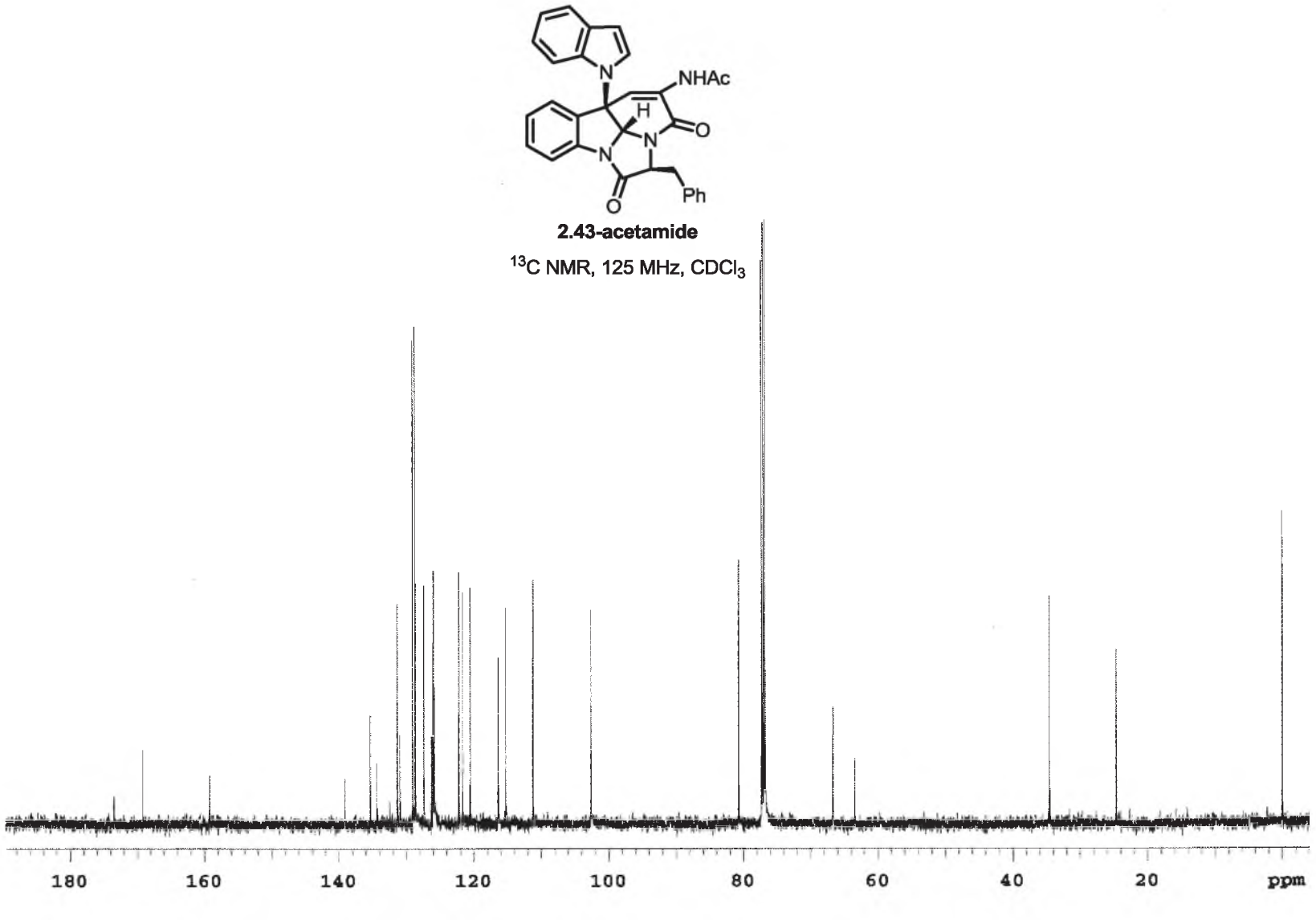


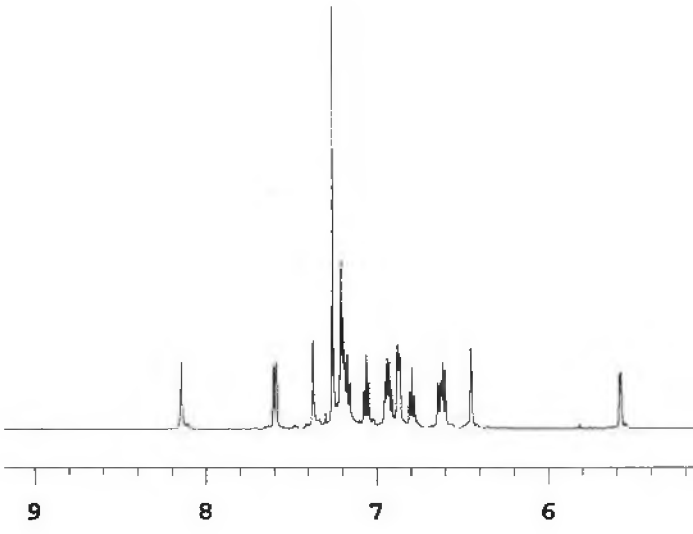
2.43-acetamide

^{1}H NMR, 500 MHz, $CDCl_3$



2.43-acetamide

^{13}C NMR, 125 MHz, $CDCl_3$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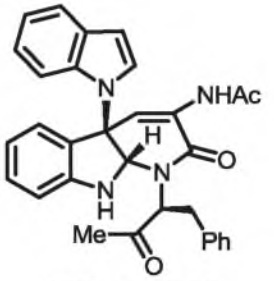
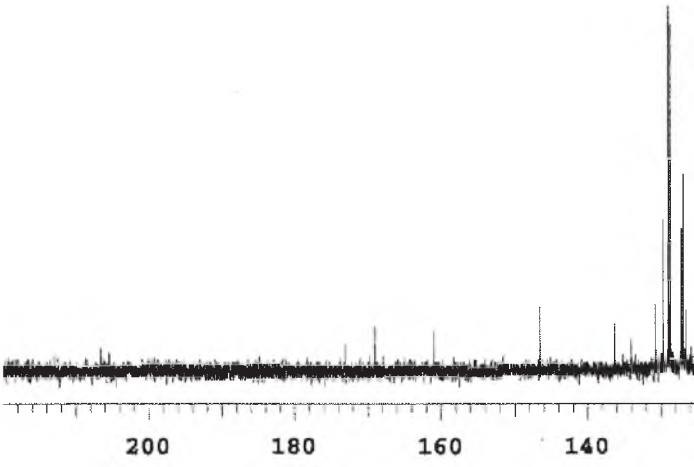


2.44-acetamide

^{1}H NMR, 500 MHz, $CDCl_3$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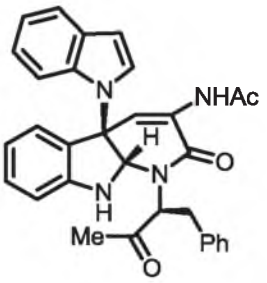
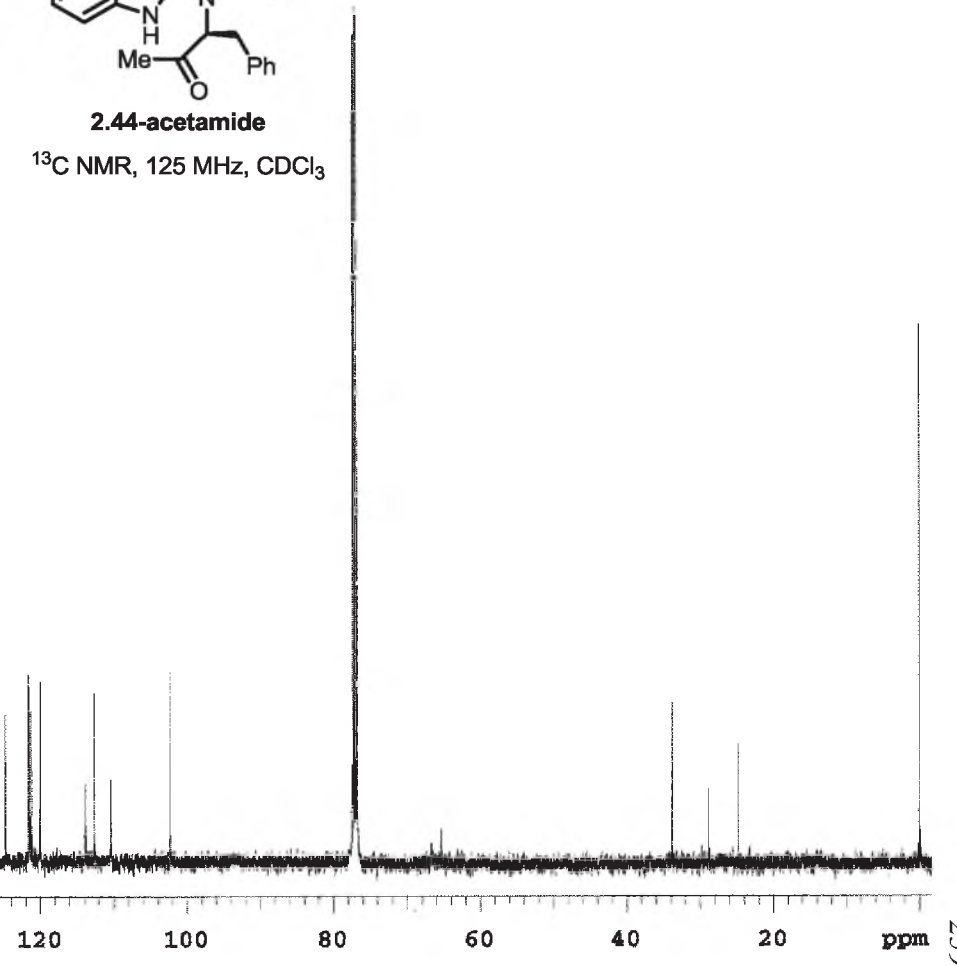
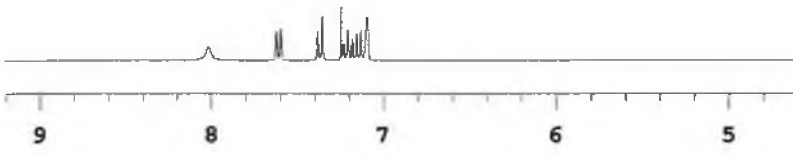


2.44-acetamide

^{13}C NMR, 125 MHz, $CDCl_3$

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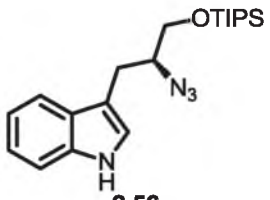


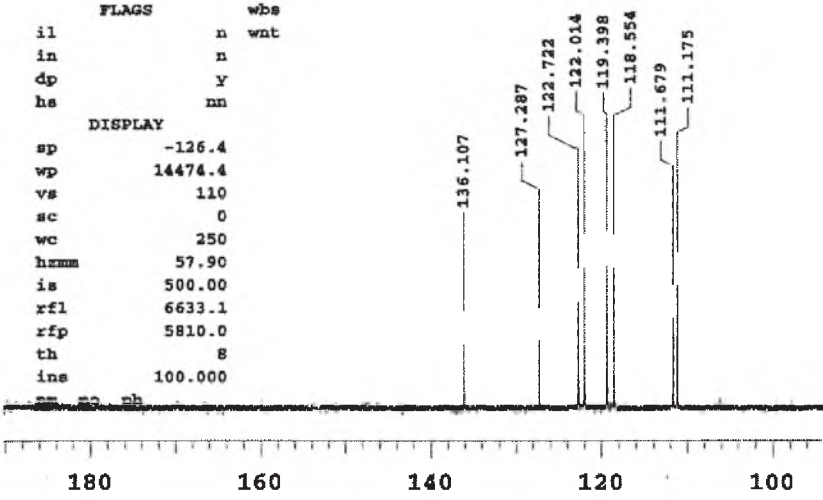
2.56

^{1}H NMR, 300 MHz, $CDCl_3$

13C OBSERVE

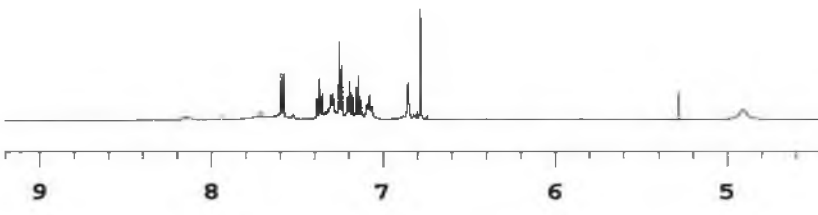
exp1 std13c

SAMPLE		DEC. & VT	
date	Dec 6 2009	dfrq	300.078
solvent	CDCl3	dn	H1
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	75.462	dm	YYY
tn	C13	dmm	w
at	3.878	dmf	11200
np	128000	dseq	
sw	16501.7	dres	1.0
fb	9200	homo	n
bs	1	PROCESSING	
tpwr	55	lb	1.00
pw	5.0	wtfile	
d1	0	proc	ft
tof	0	fn	not used
nt	1024	math	f
ct	33		
alock	n	werr	
gain	6	wexp	
FLAGS		wbs	
il	n	wnt	
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-126.4		
wp	14474.4		
vs	110		
sc	0		
wc	250		
hzmm	57.90		
is	500.00		
rfl	6633.1		
rfp	5810.0		
th	8		
ins	100.000		



2.56

^{13}C NMR, 75 MHz, $CDCl_3$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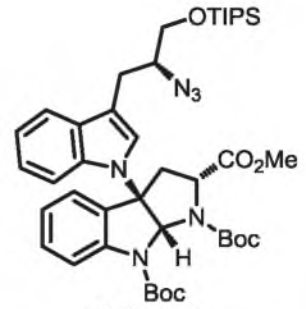
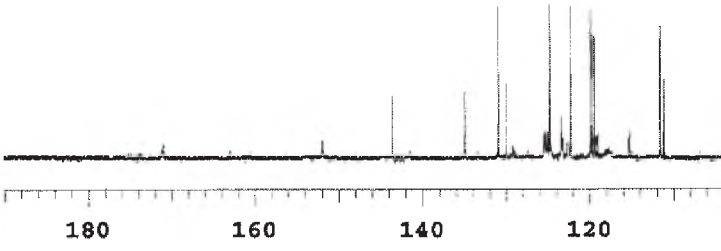


2.57-*endo*

^{1}H NMR, 500 MHz, $CDCl_3$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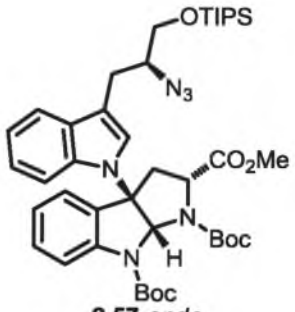
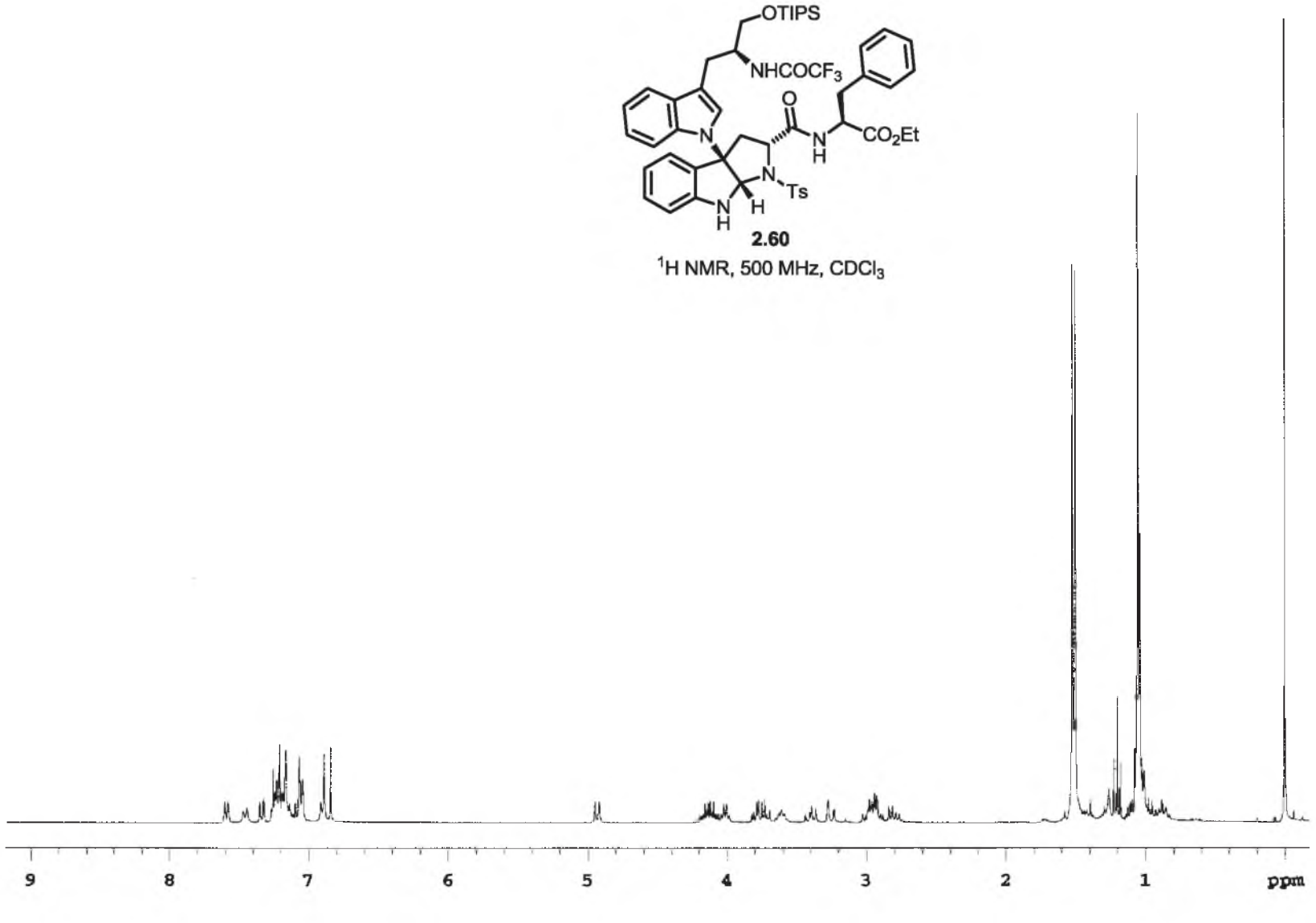


2.57-*endo*

^{13}C NMR, 125 MHz, $CDCl_3$


OTIPS
NHCOCF3
O
N
H
CO2Et
N
Ts
N
H
H
2.60
1H NMR, 500 MHz, CDCl3
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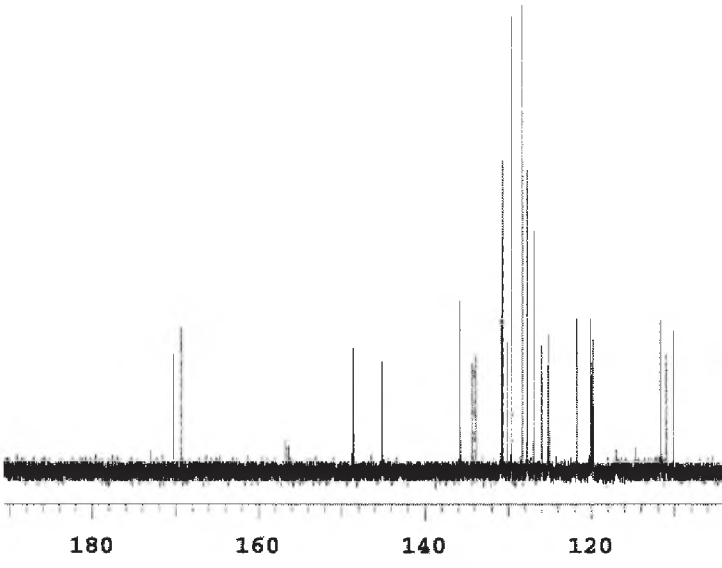
4
3
2
1
ppm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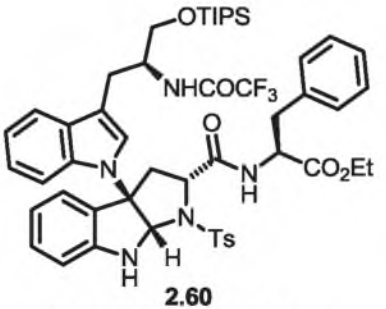
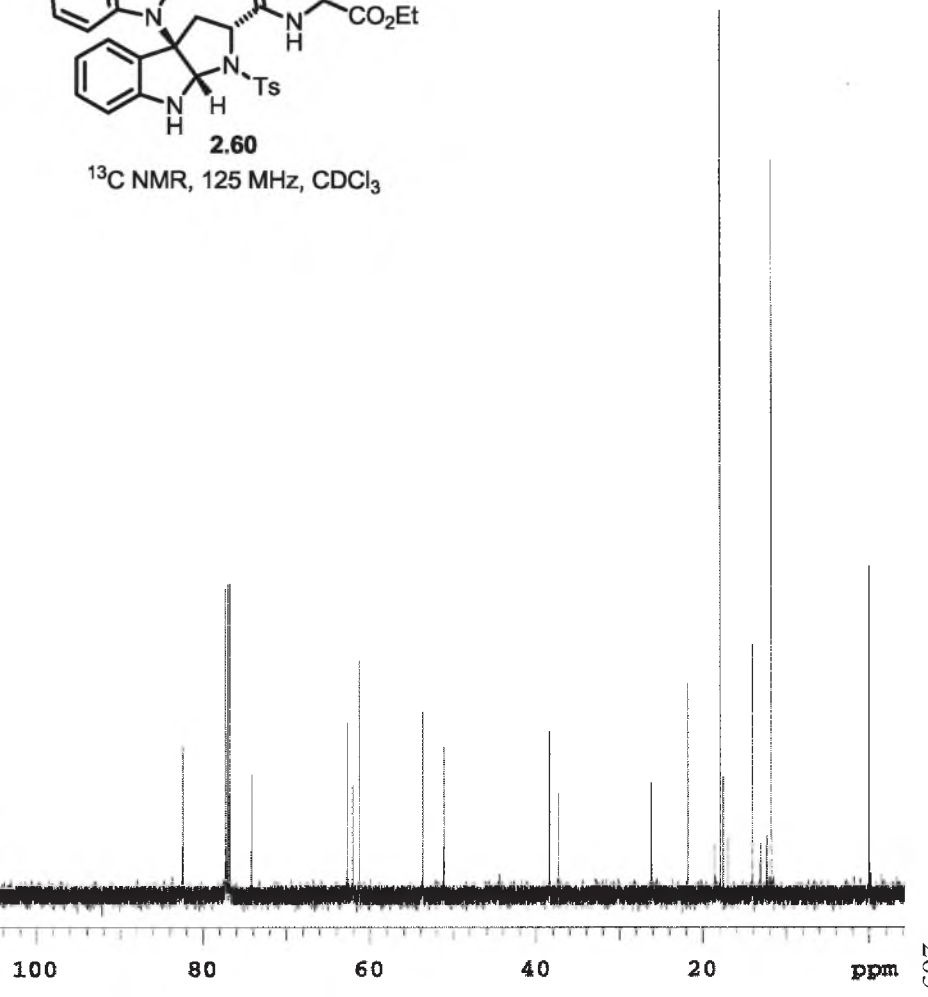
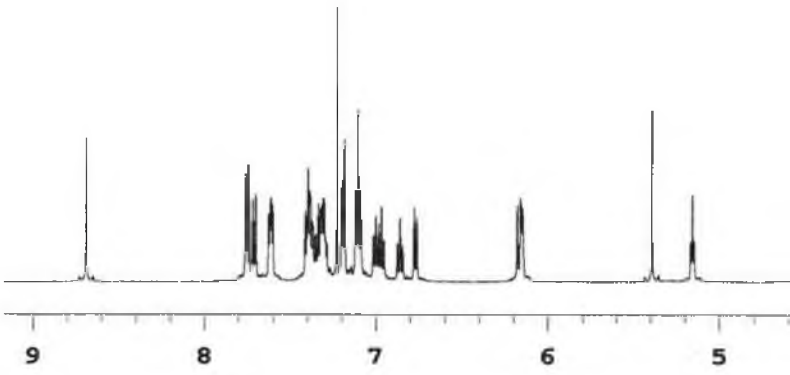


2.60

^{13}C NMR, 125 MHz, $CDCl_3$

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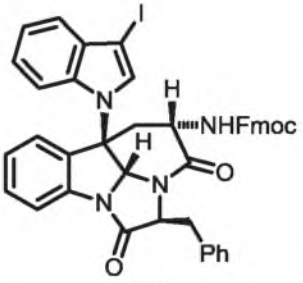
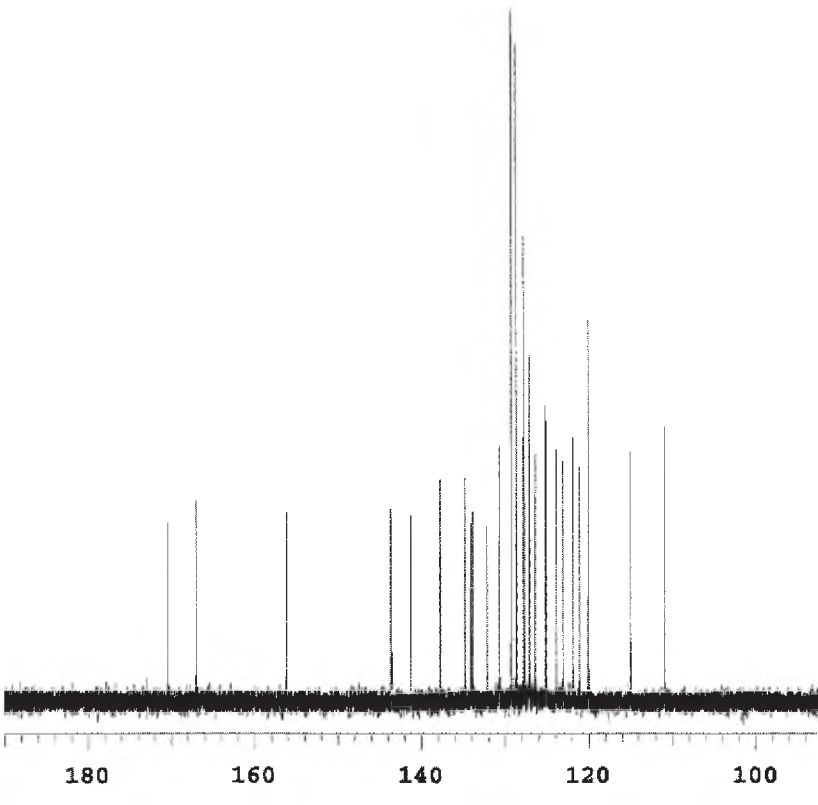


2.69

^{1}H NMR, 500 MHz, $CDCl_3$


180
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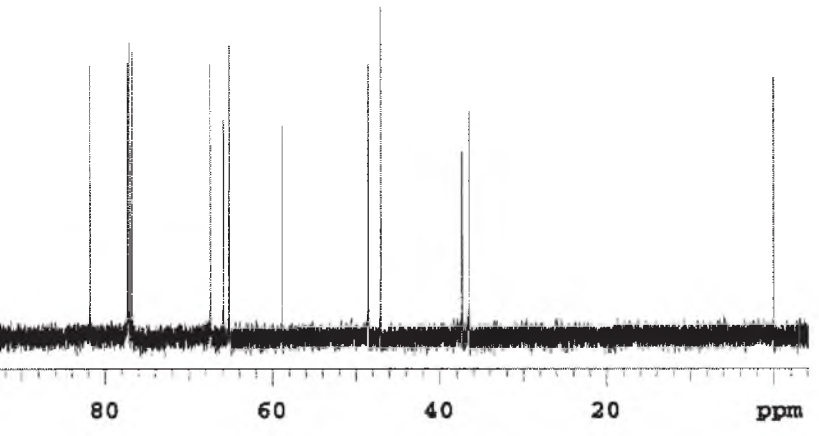
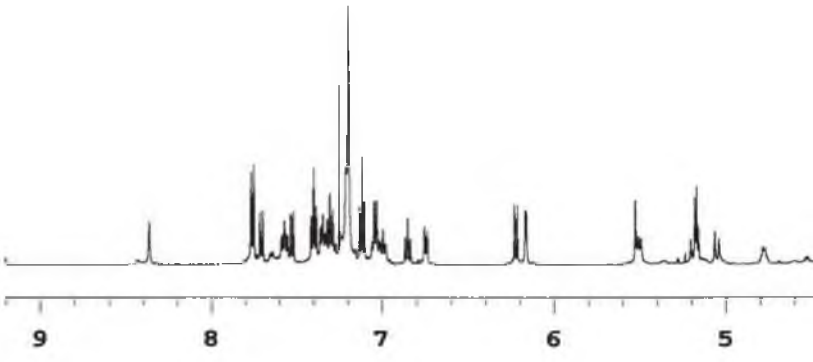
2.69

^{13}C NMR, 125 MHz, $CDCl_3$

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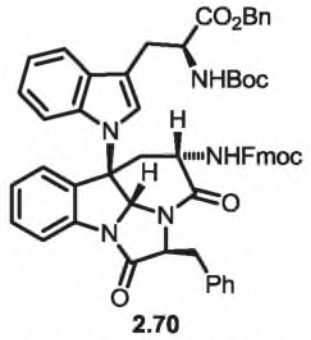
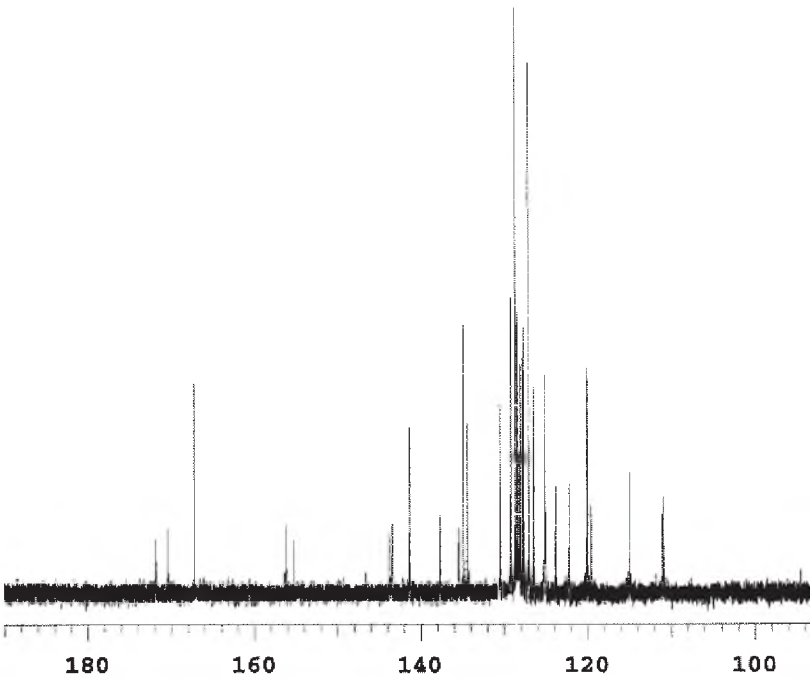


2.70

^{1}H NMR, 500 MHz, $CDCl_3$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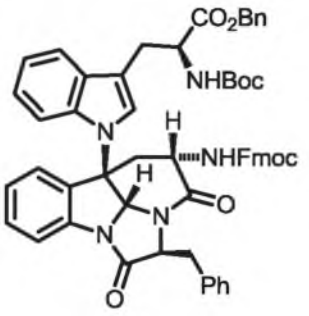
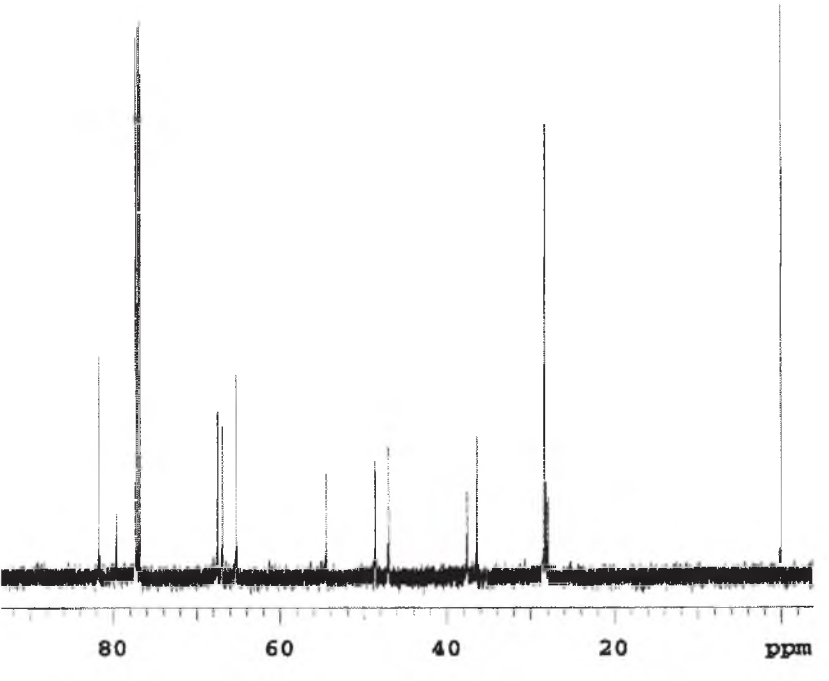


2.70

^{13}C NMR, 125 MHz, $CDCl_3$

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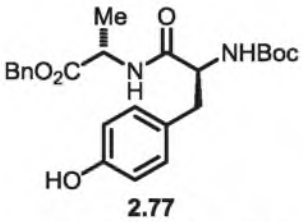
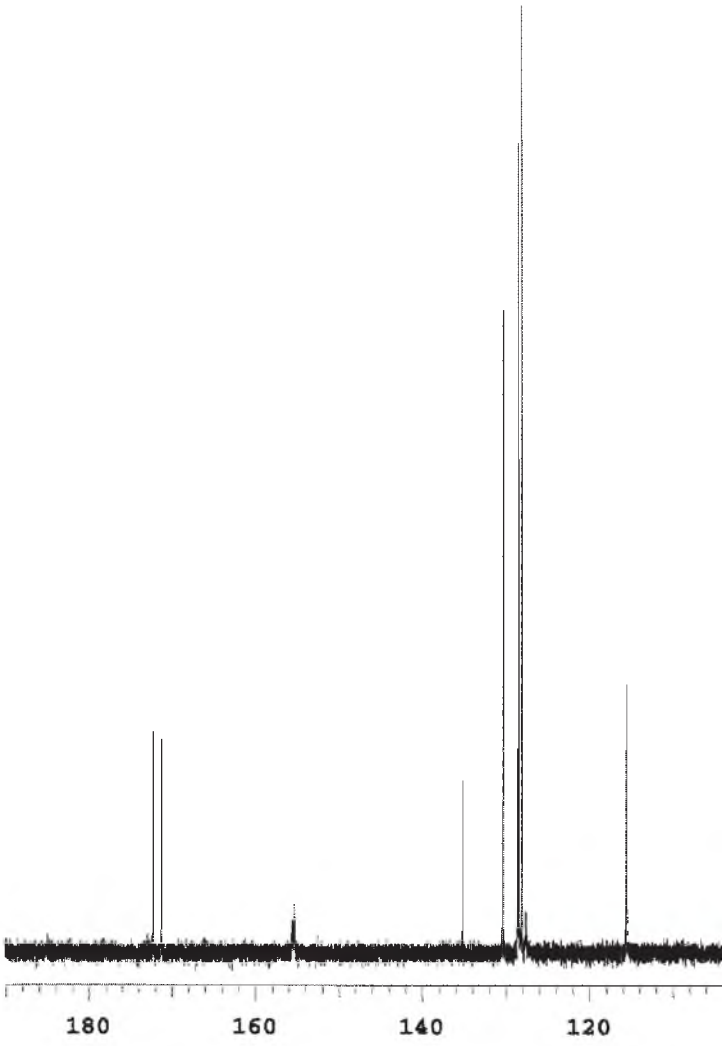


2.77

^{1}H NMR, 500 MHz, $CDCl_3$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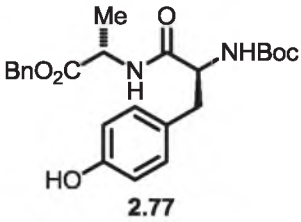
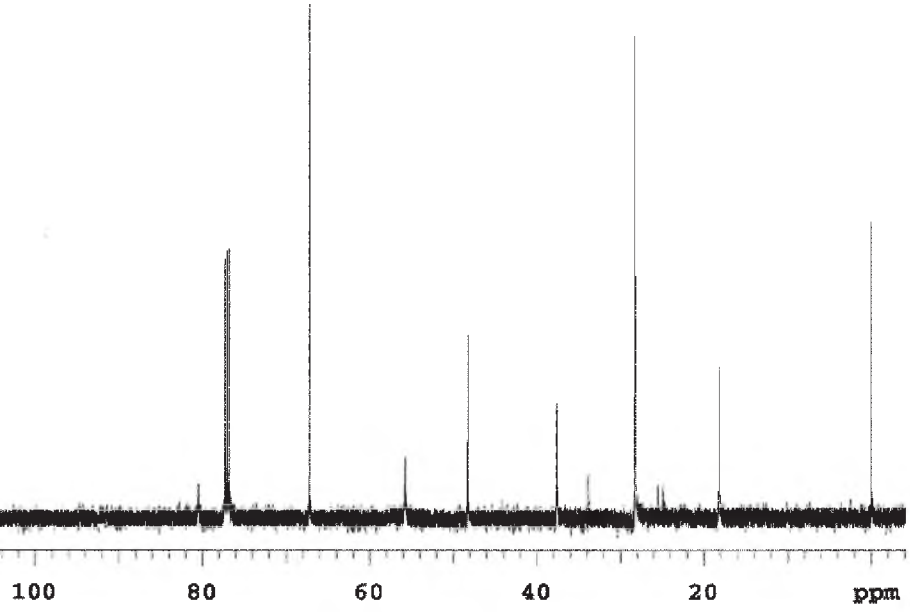
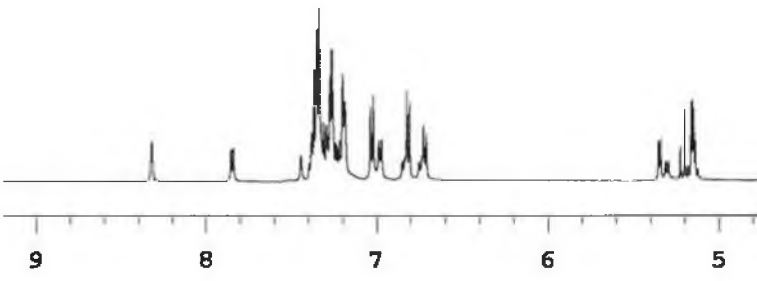


2.77

^{13}C NMR, 125 MHz, $CDCl_3$

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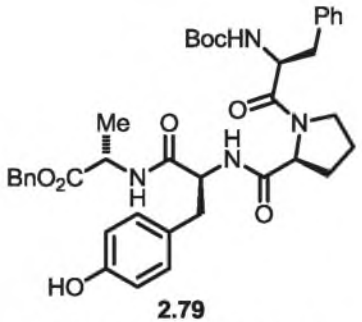
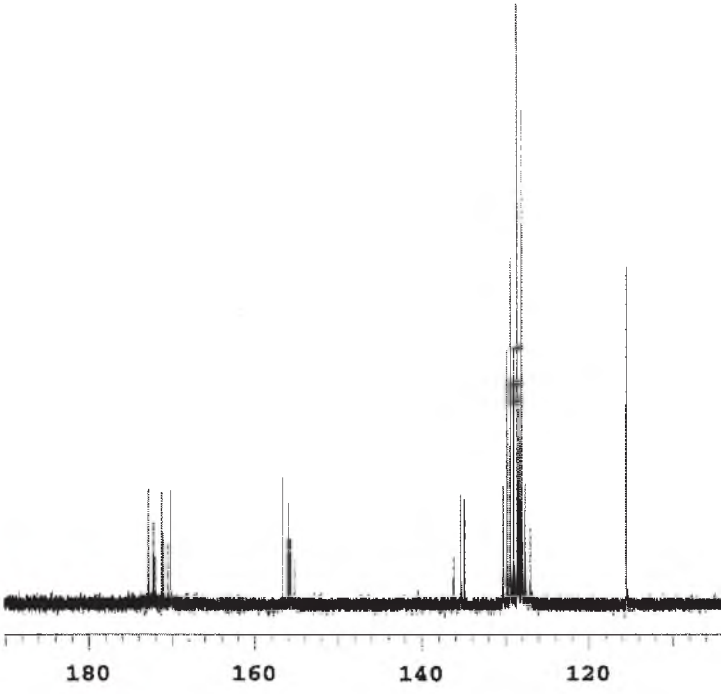


2.79

^{1}H NMR, 500 MHz, $CDCl_3$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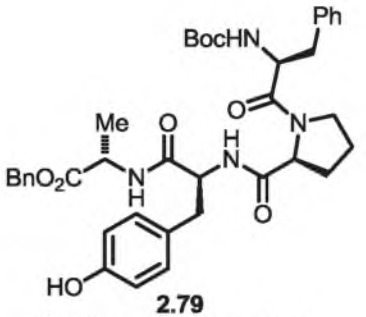
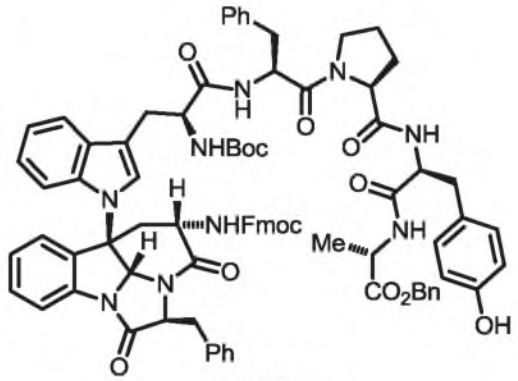


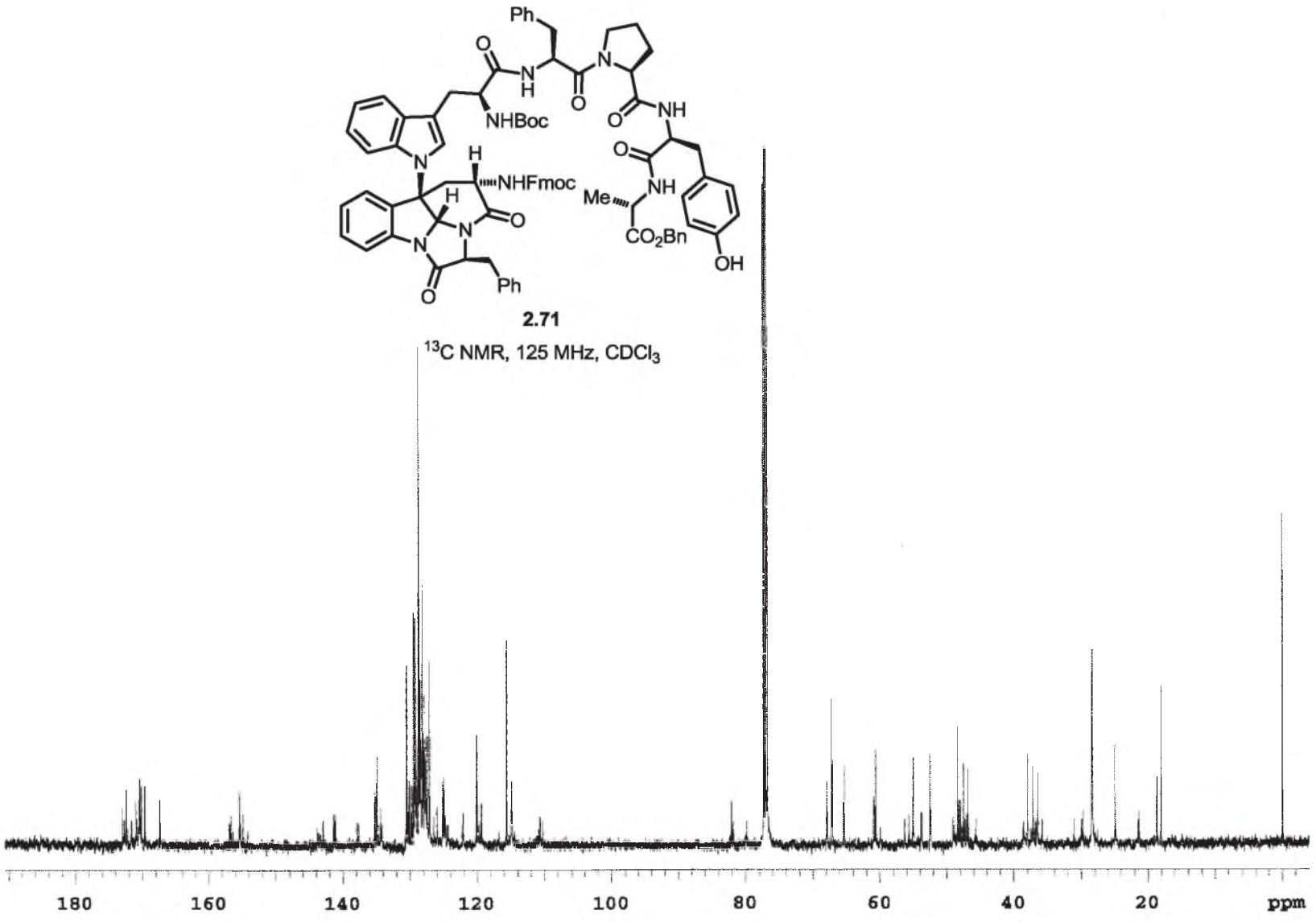
2.79

^{13}C NMR, 125 MHz, $CDCl_3$

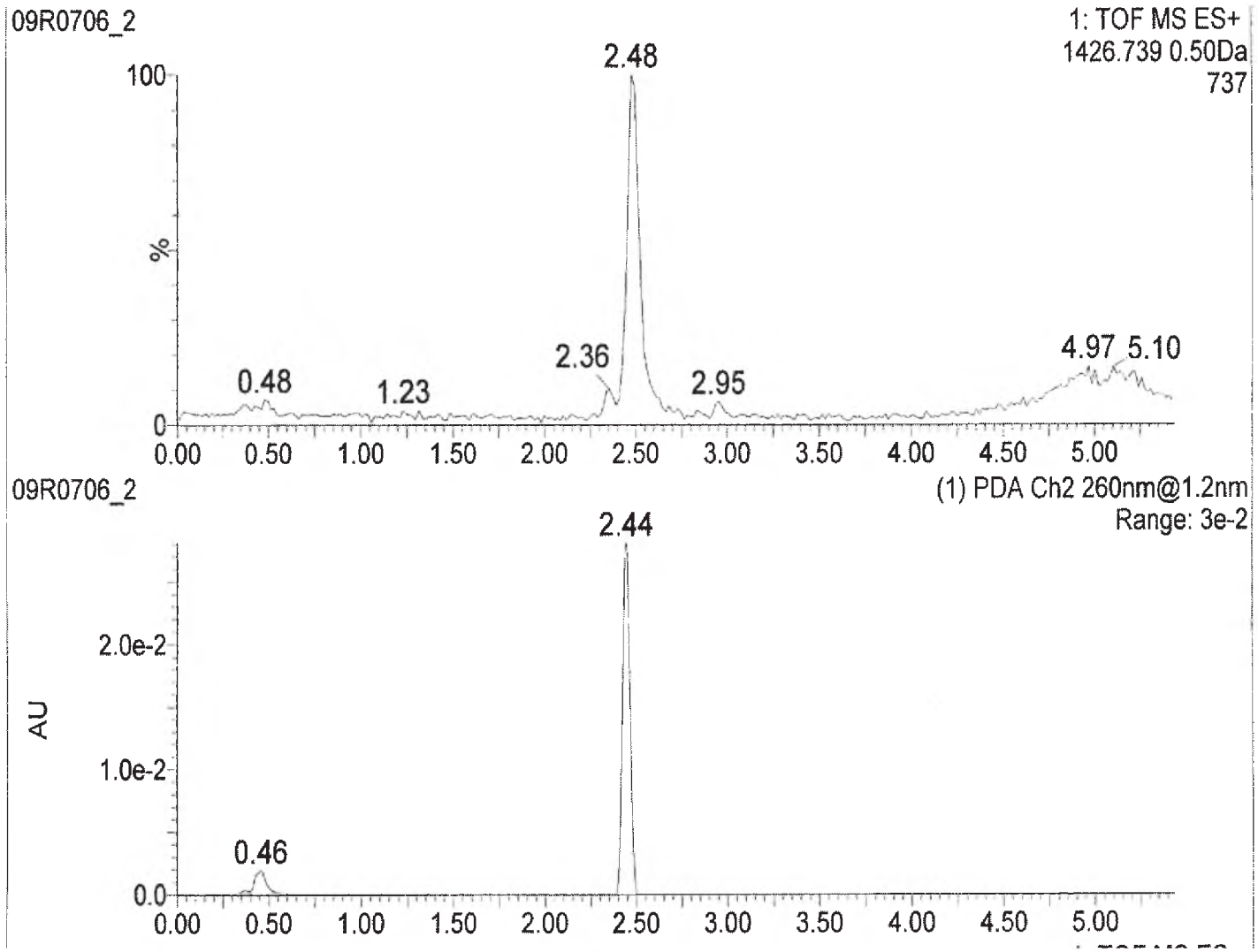


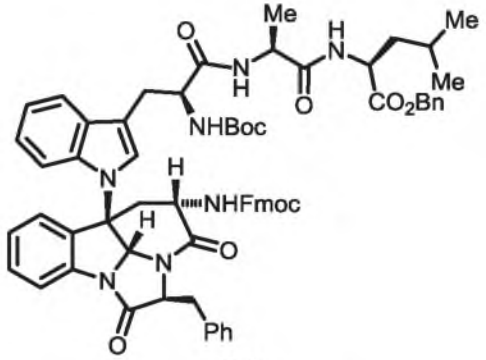
2.71

^{1}H NMR, 500 MHz; $CDCl_3$


Ph
O
N
H
O
N
NHBoc
O
NH
H
N
NHFmoc
O
Me
NH
H
N
N
O
CO2Bn
OH
O
Ph
2.71
13C NMR, 125 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm

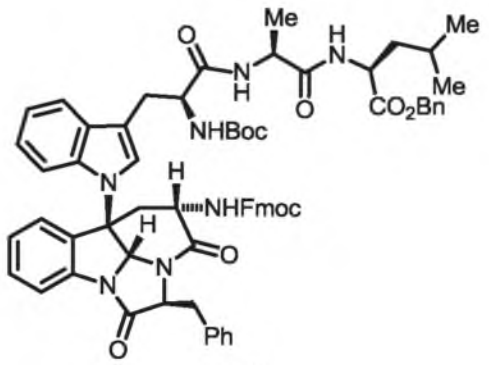
LC/MS Analysis of **2.71**





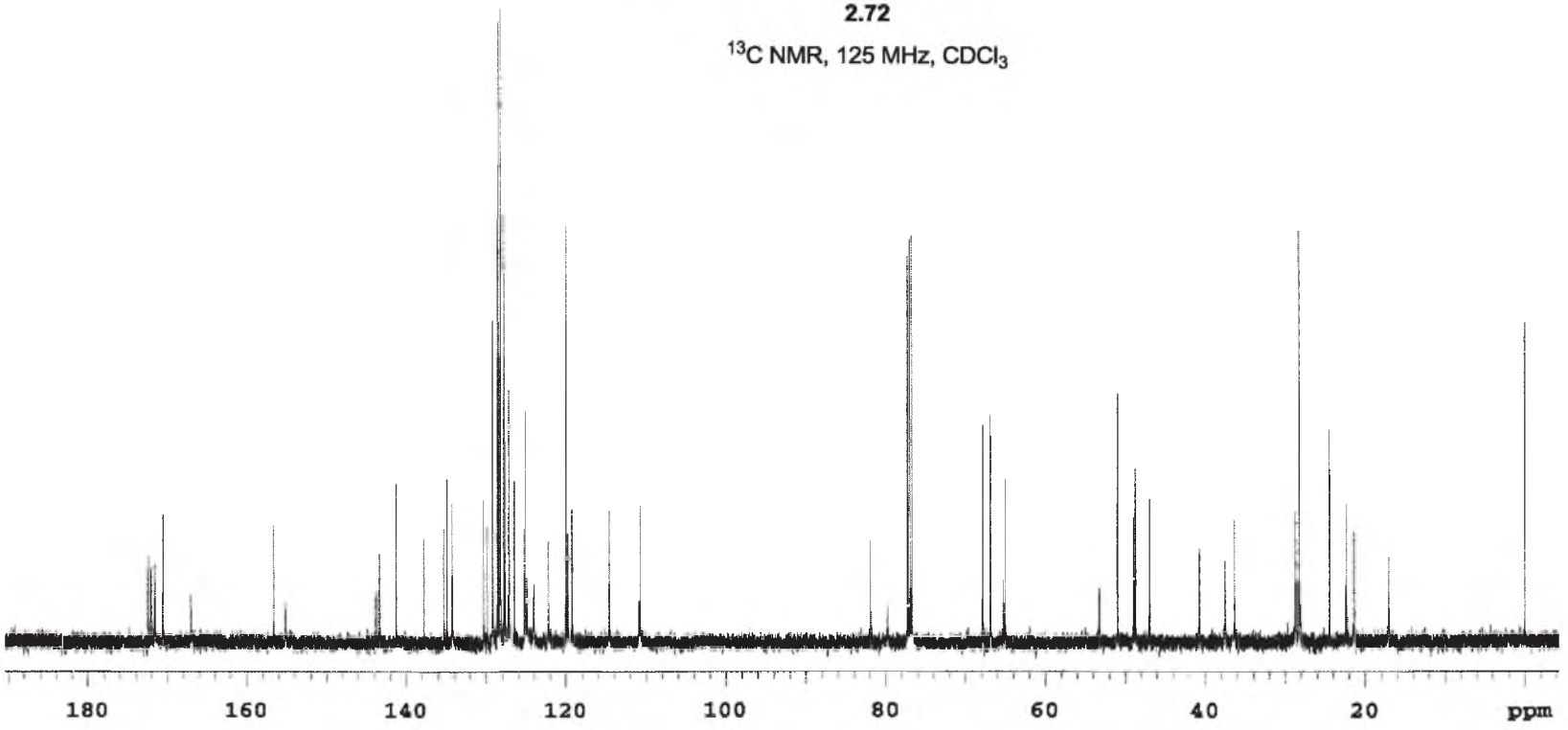
2.72

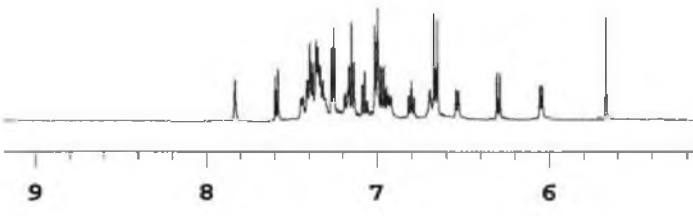
^{1}H NMR, 500 MHz, $CDCl_3$

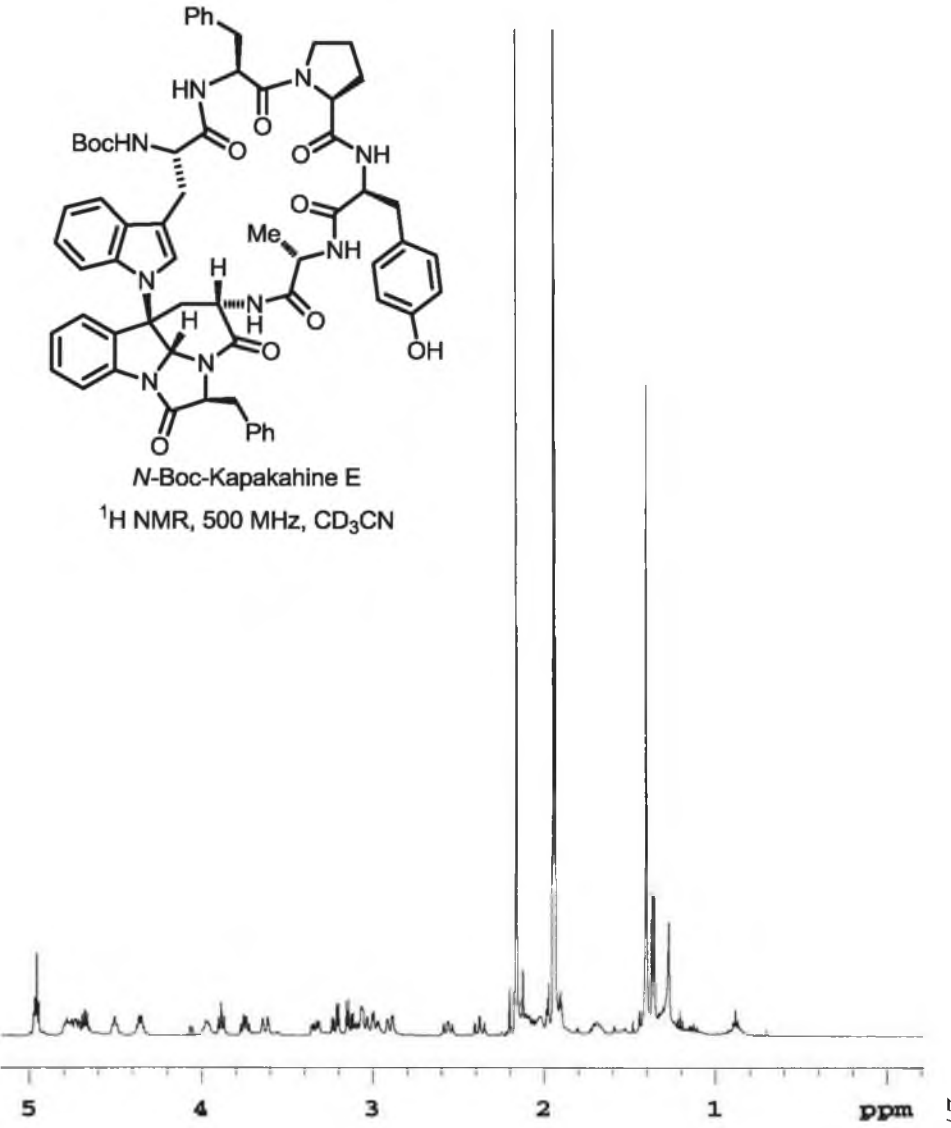


2.72

^{13}C NMR, 125 MHz, $CDCl_3$




9
8
7
6



N-Boc-Kapakahine E

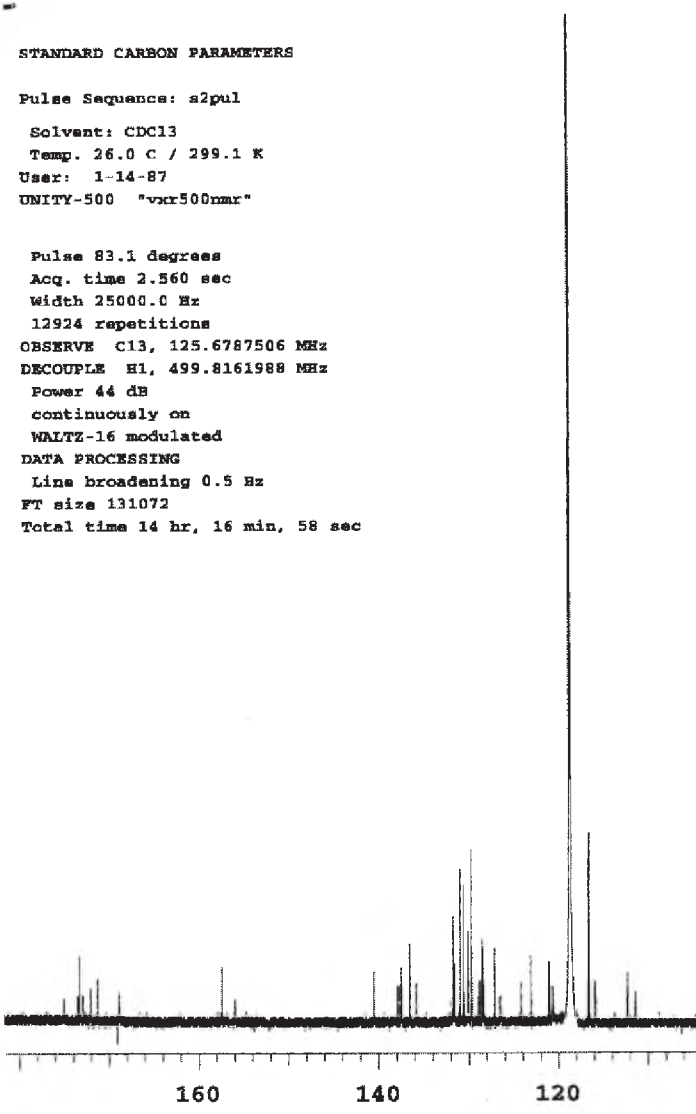
^{1}H NMR, 500 MHz, CD_3CN

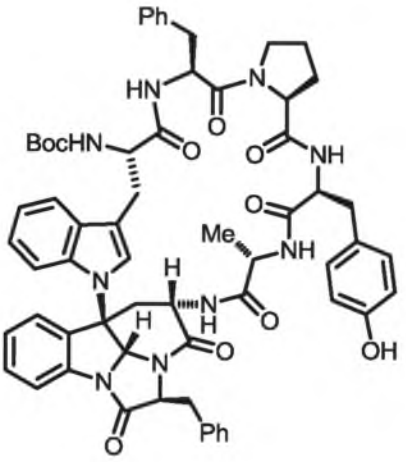
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 26.0 C / 299.1 K
User: 1-14-87
UNITY-500 "vxr500nmr"

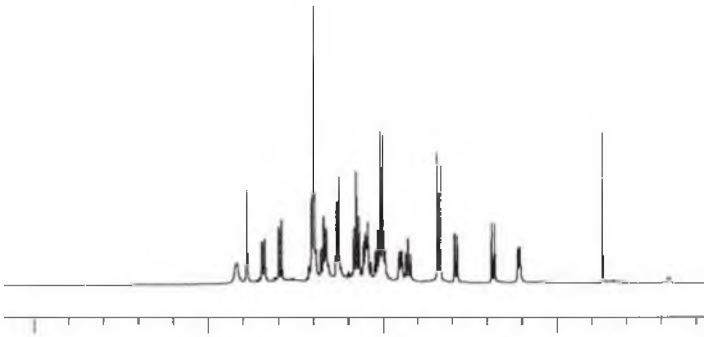
Pulse 83.1 degrees
Acq. time 2.560 sec
Width 25000.0 Hz
12924 repetitions
OBSERVE C13, 125.6787506 MHz
DECOUPLE H1, 499.8161988 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 14 hr, 16 min, 58 sec

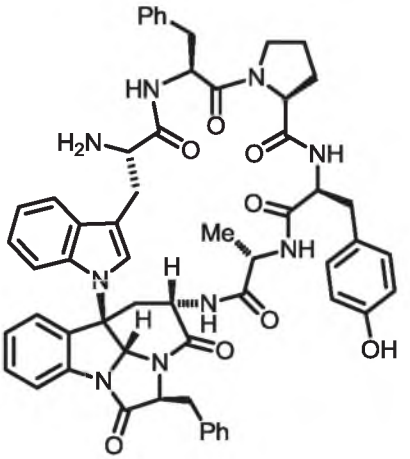




N-Boc-Kapakahine E

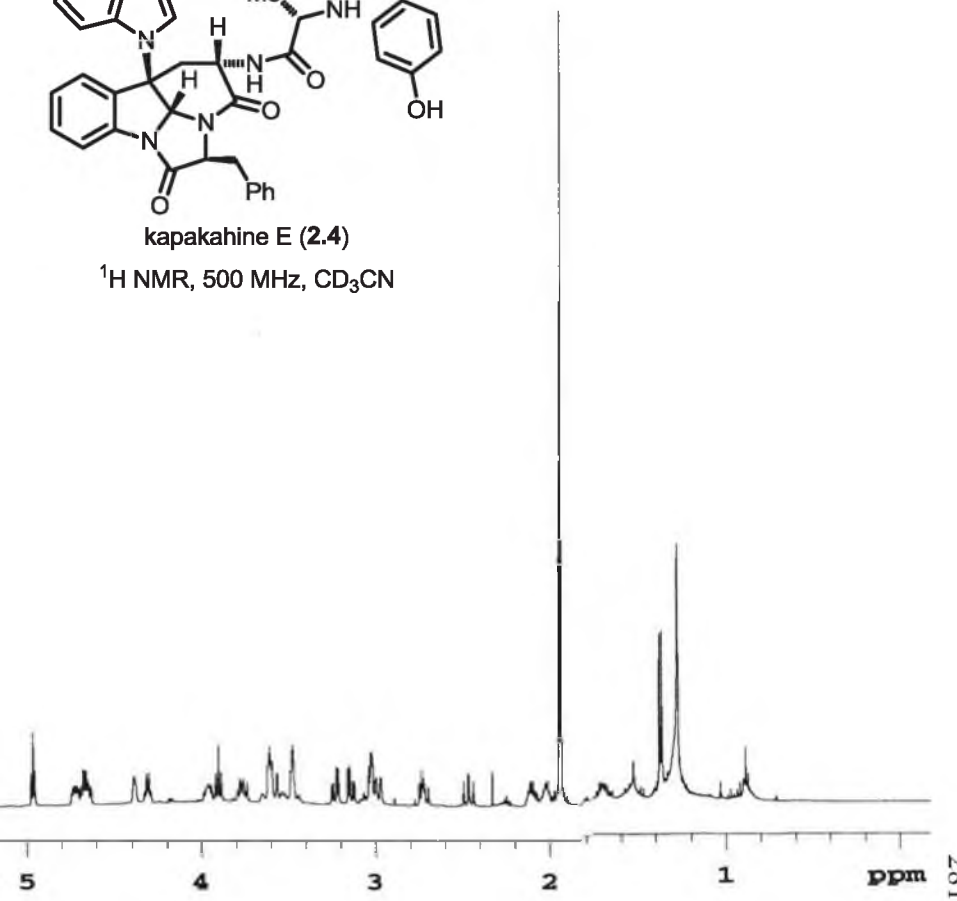
^{13}C NMR, 125 MHz, CD_3CN

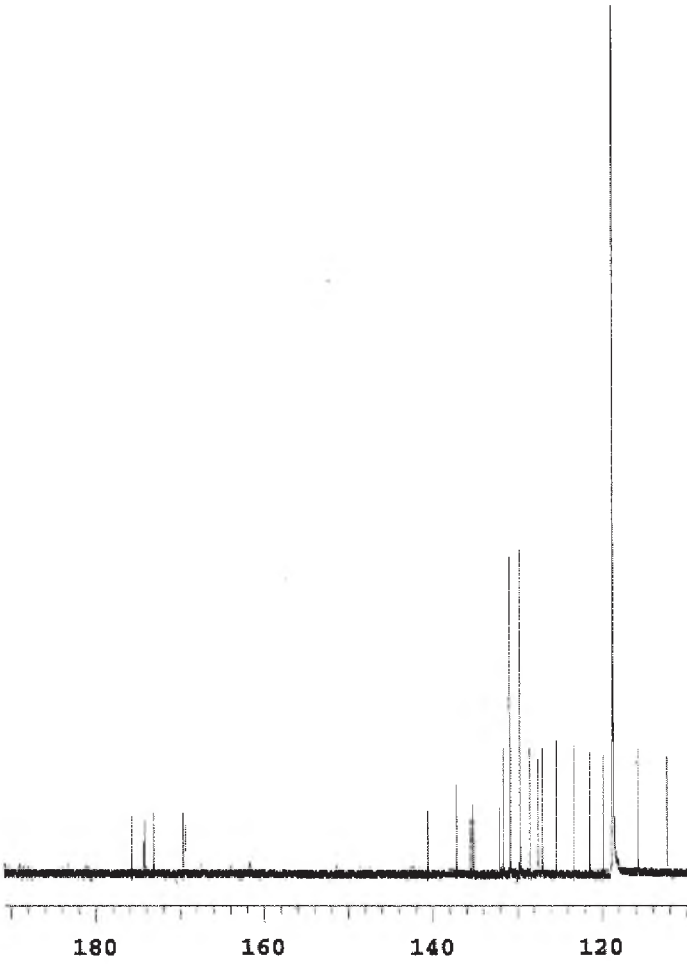

9
8
7
6

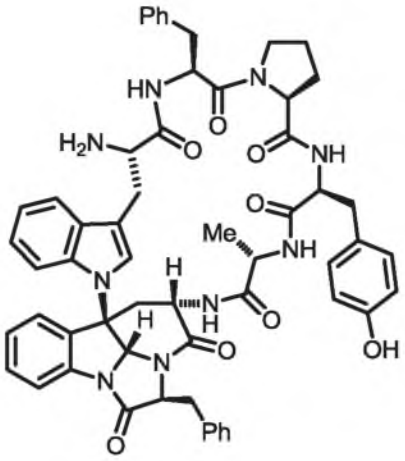


kapakahine E (**2.4**)

^{1}H NMR, 500 MHz, CD_3CN

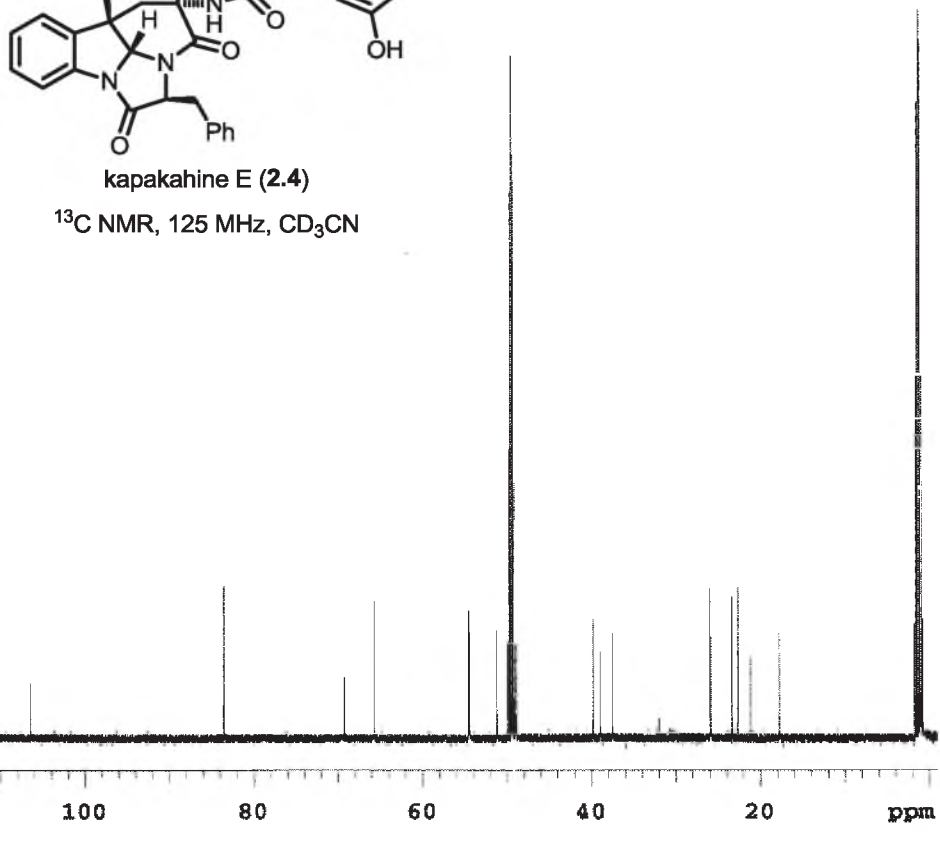



180
160
140
120

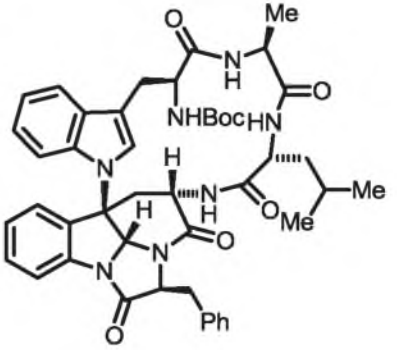


kapakahine E (**2.4**)

^{13}C NMR, 125 MHz, CD_3CN

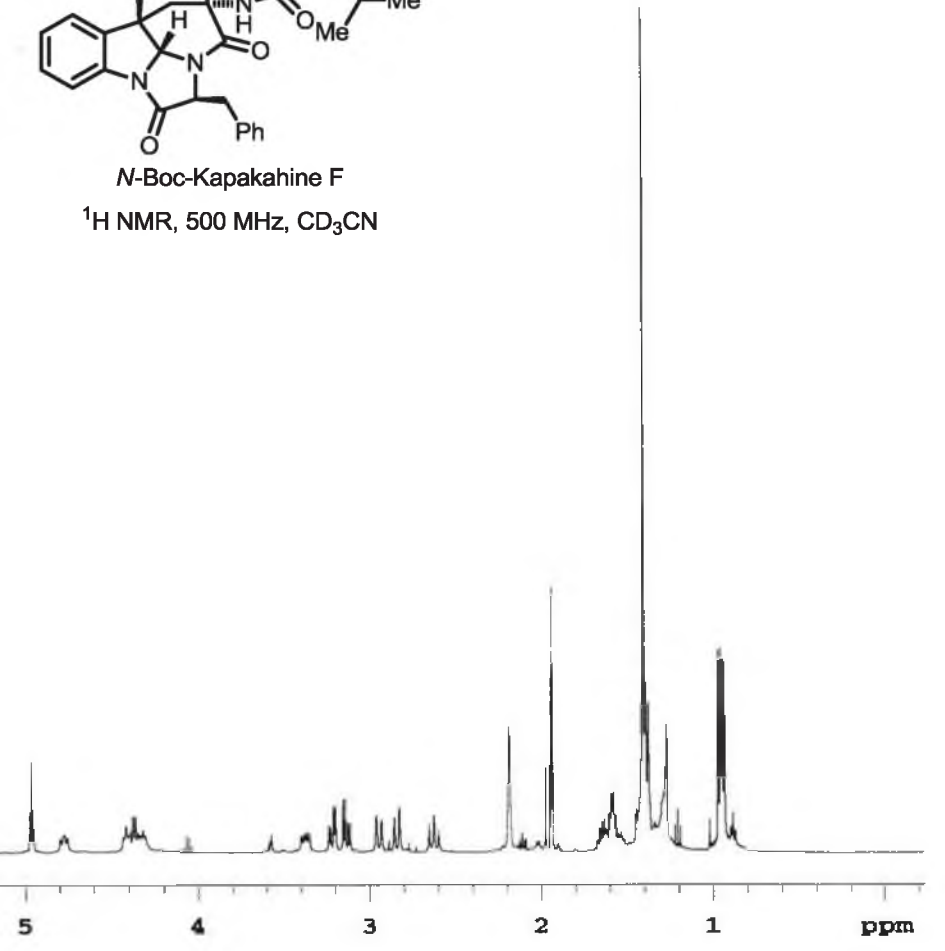


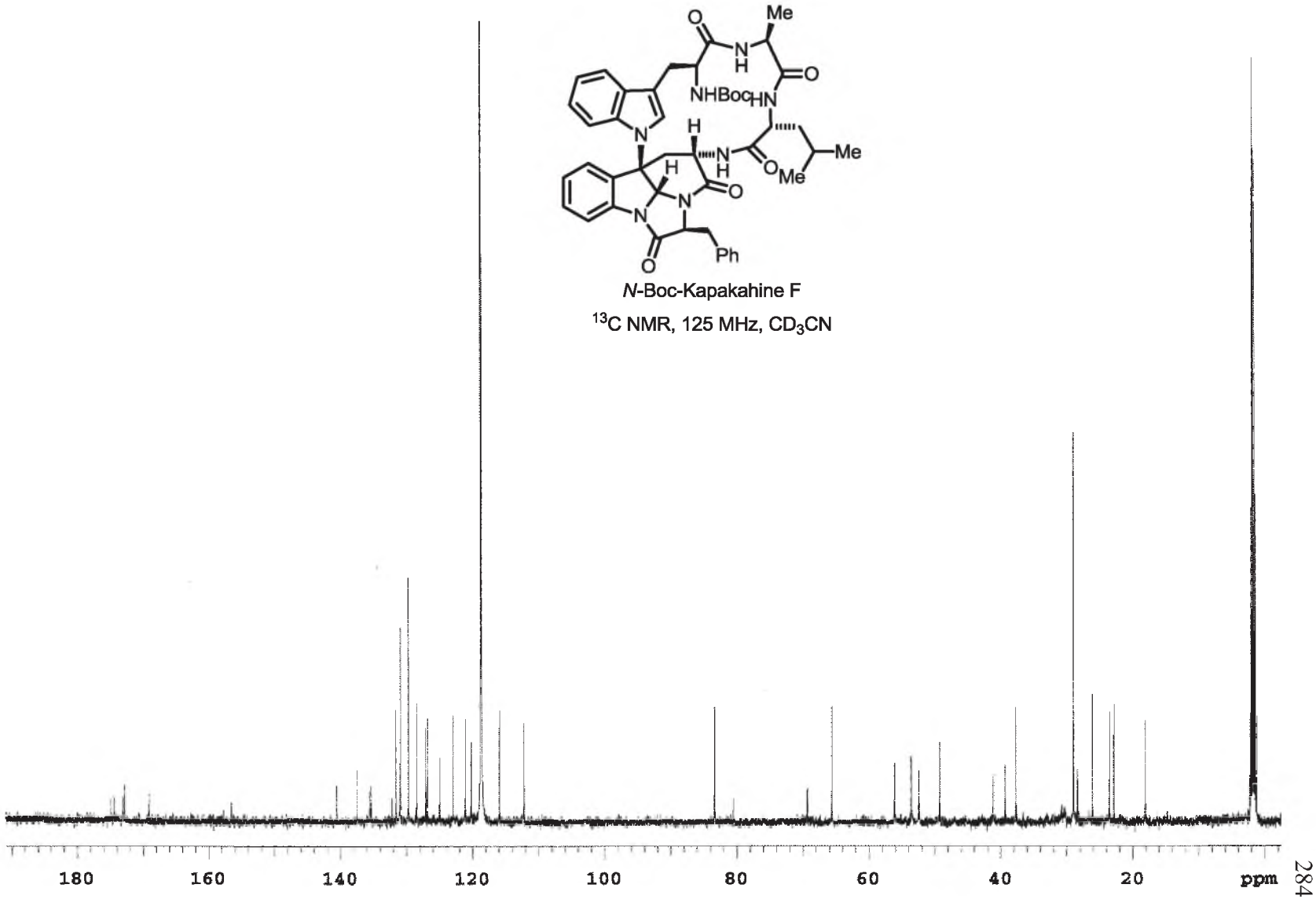

9
8
7
6



N-Boc-Kapakahine F

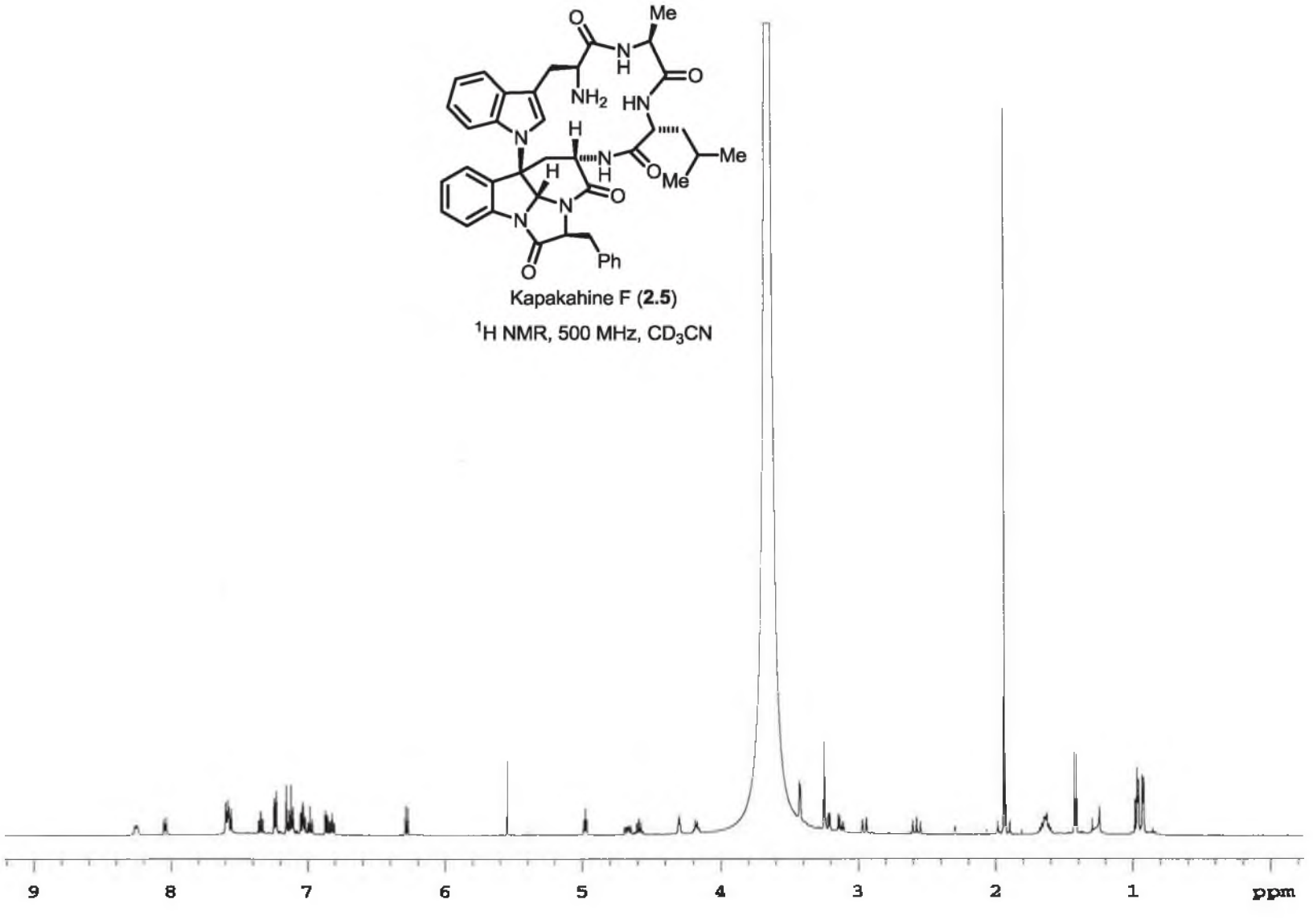
^{1}H NMR, 500 MHz, CD_3CN





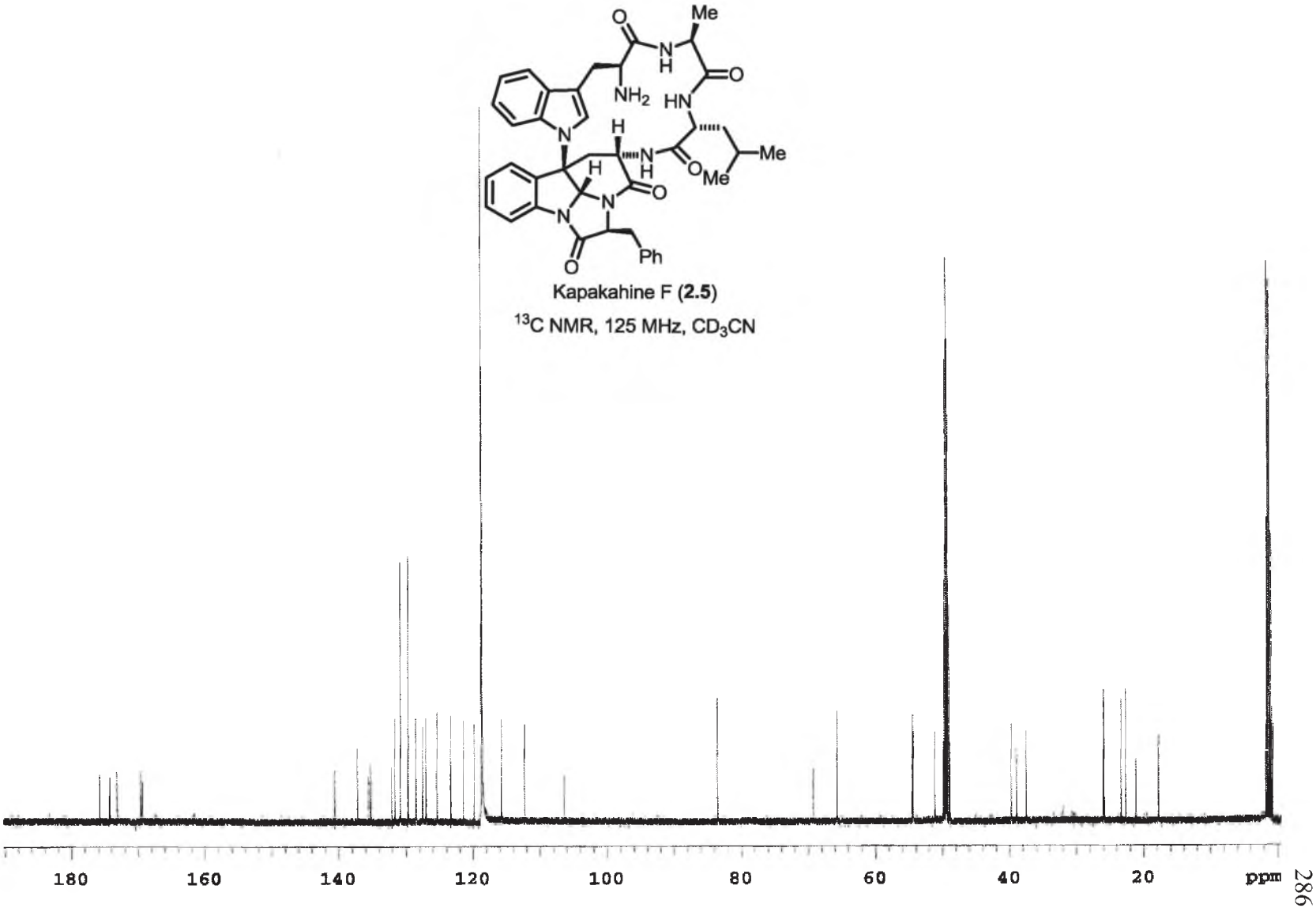
N-Boc-Kapakahine F

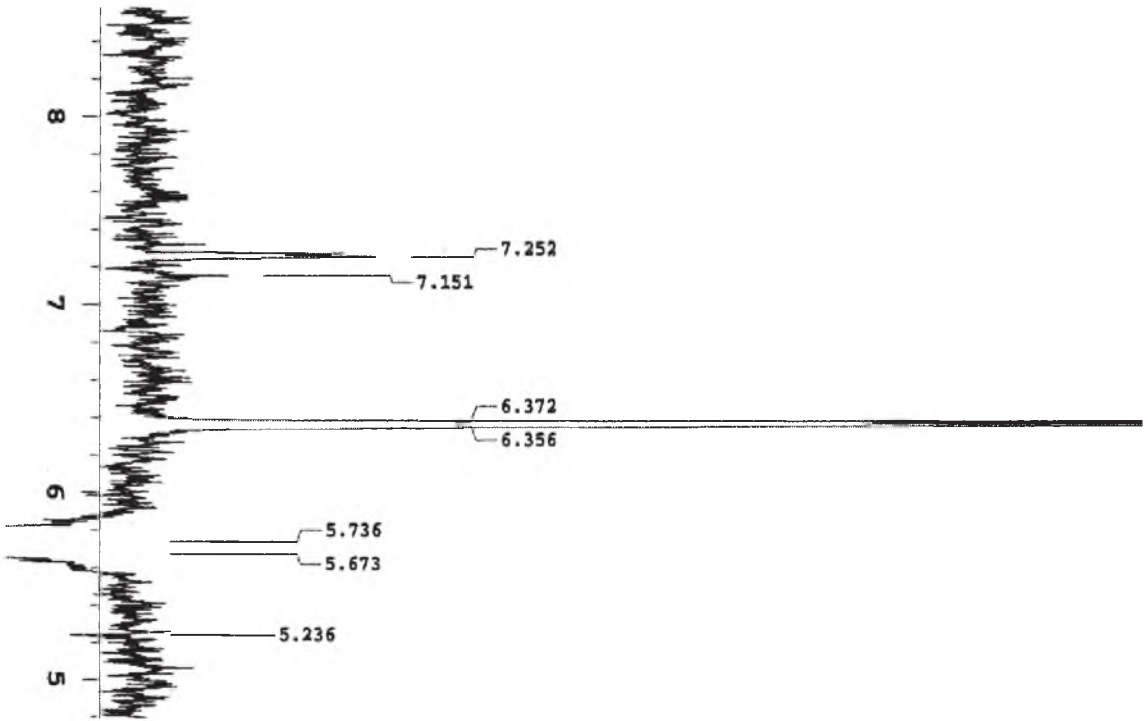
^{13}C NMR, 125 MHz, CD_3CN

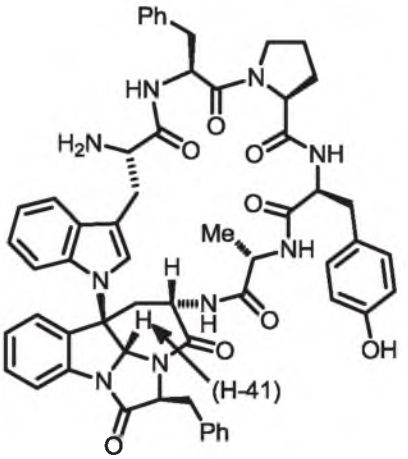


Kapakahine F (**2.5**)

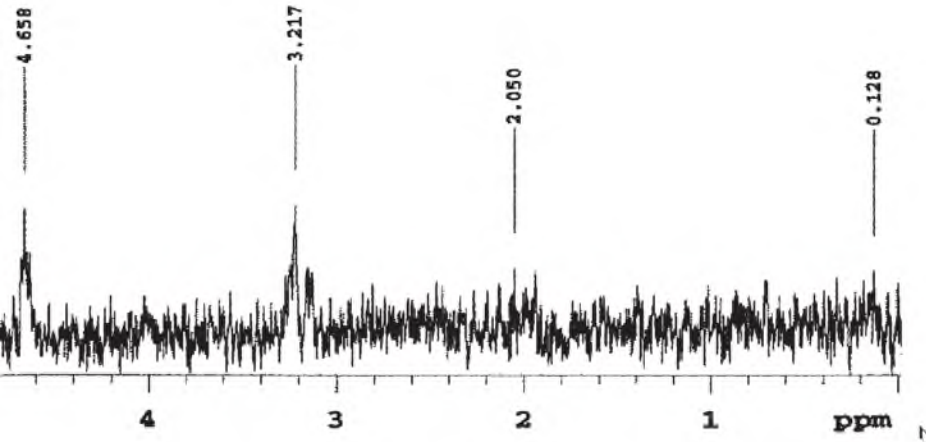
^{1}H NMR, 500 MHz, CD_3CN

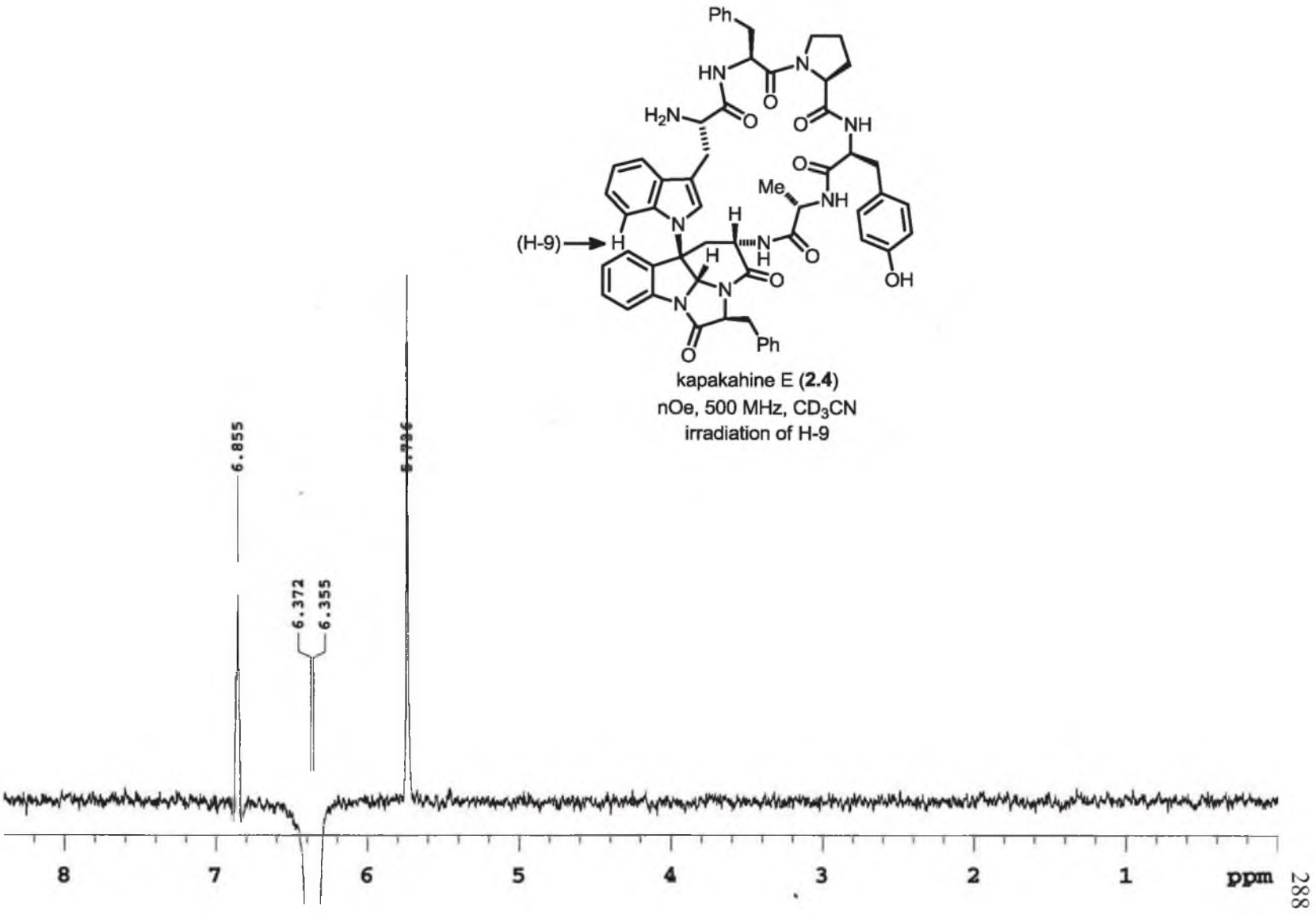

Me
O
N
H
O
NH2
HN
H
N
H
Me
Me
O
H
N
O
N
O
Ph
Kapakahine F (2.5)
13C NMR, 125 MHz, CD3CN
180
160
140
120
100
80
60
40
20
ppm


8
7
6
5
7.252
7.151
6.372
6.356
5.736
5.673
5.236

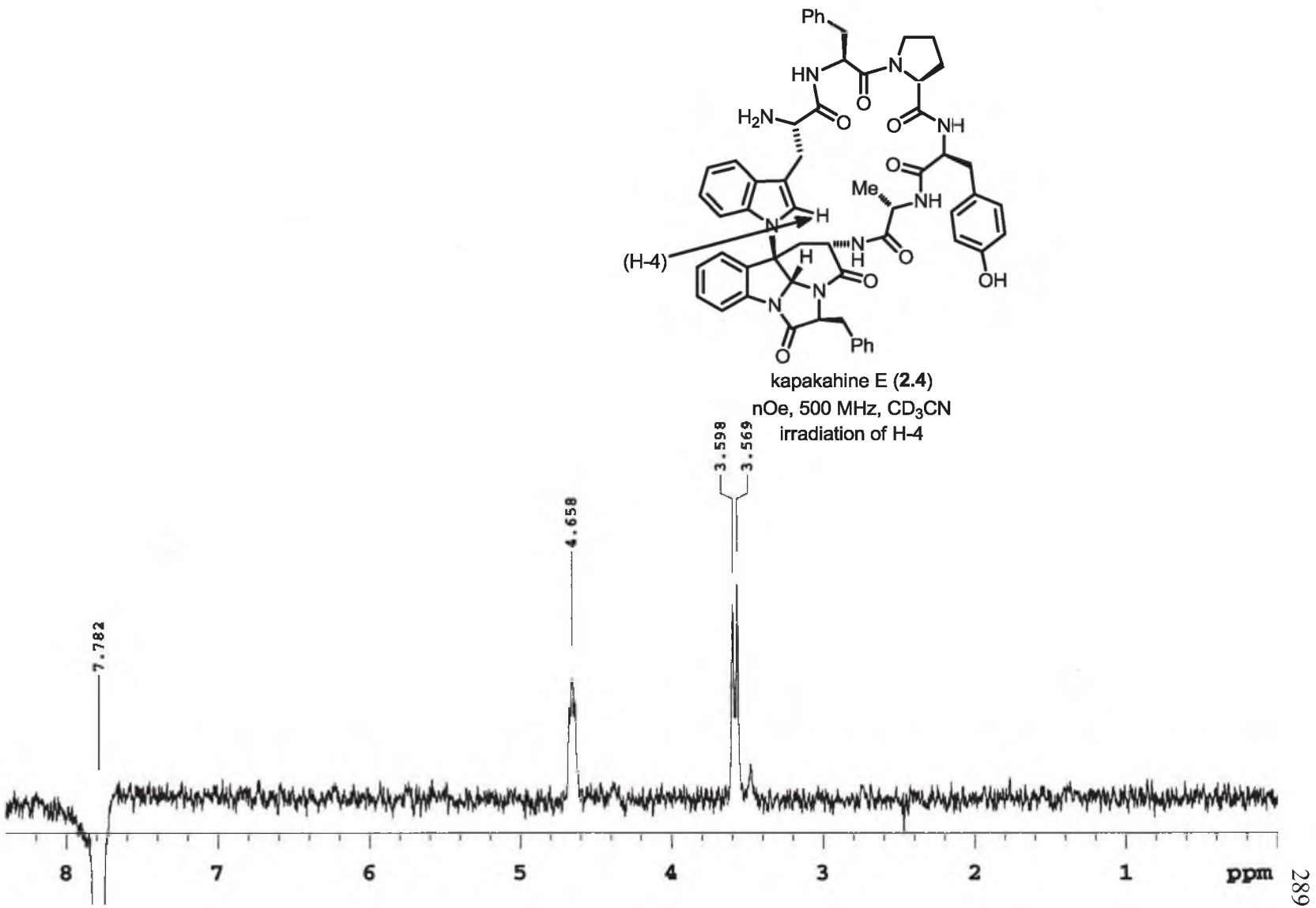


kapakahine E (**2.4**)
nOe, 500 MHz, CD_3CN
irradiation of H-41



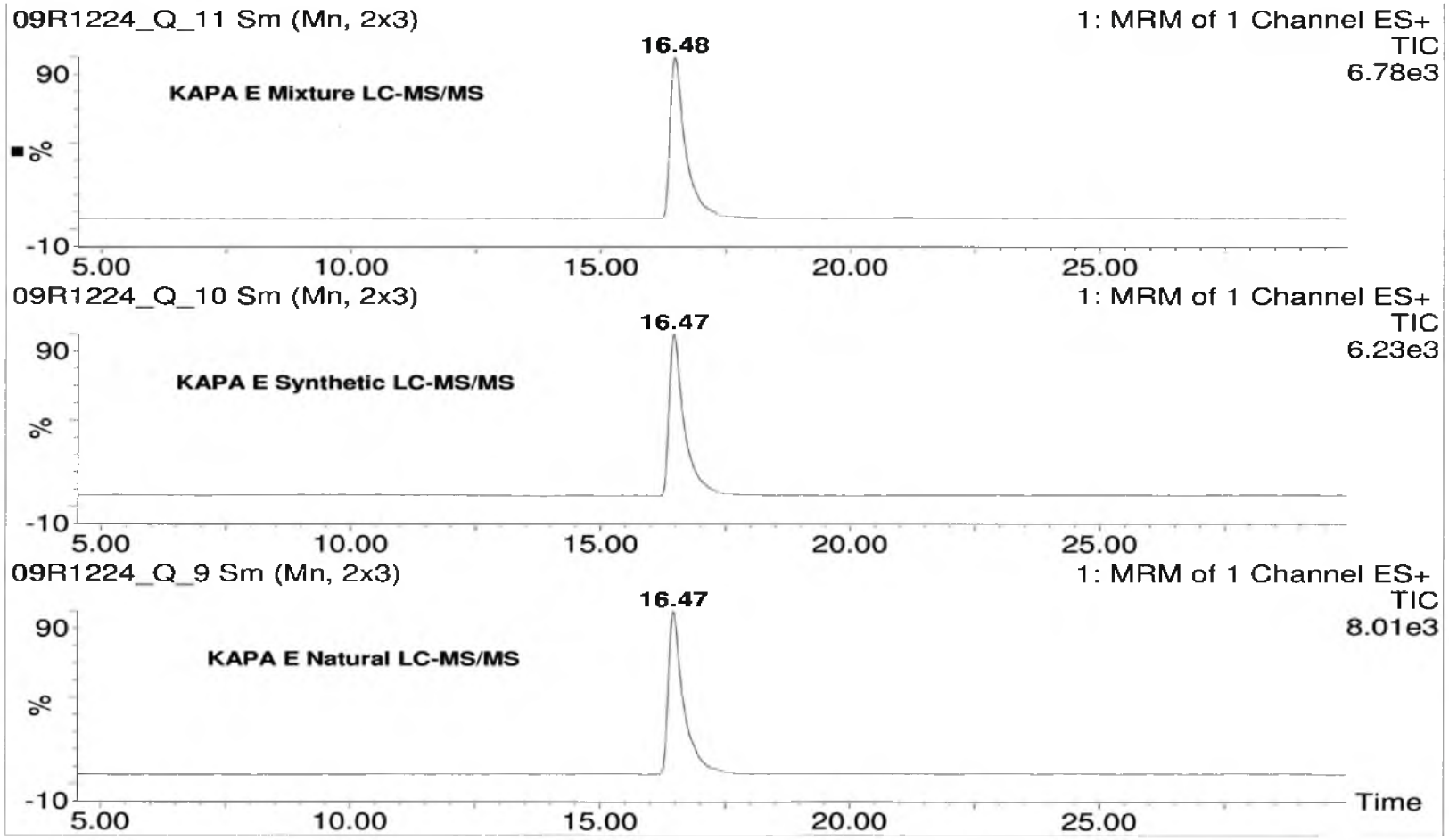


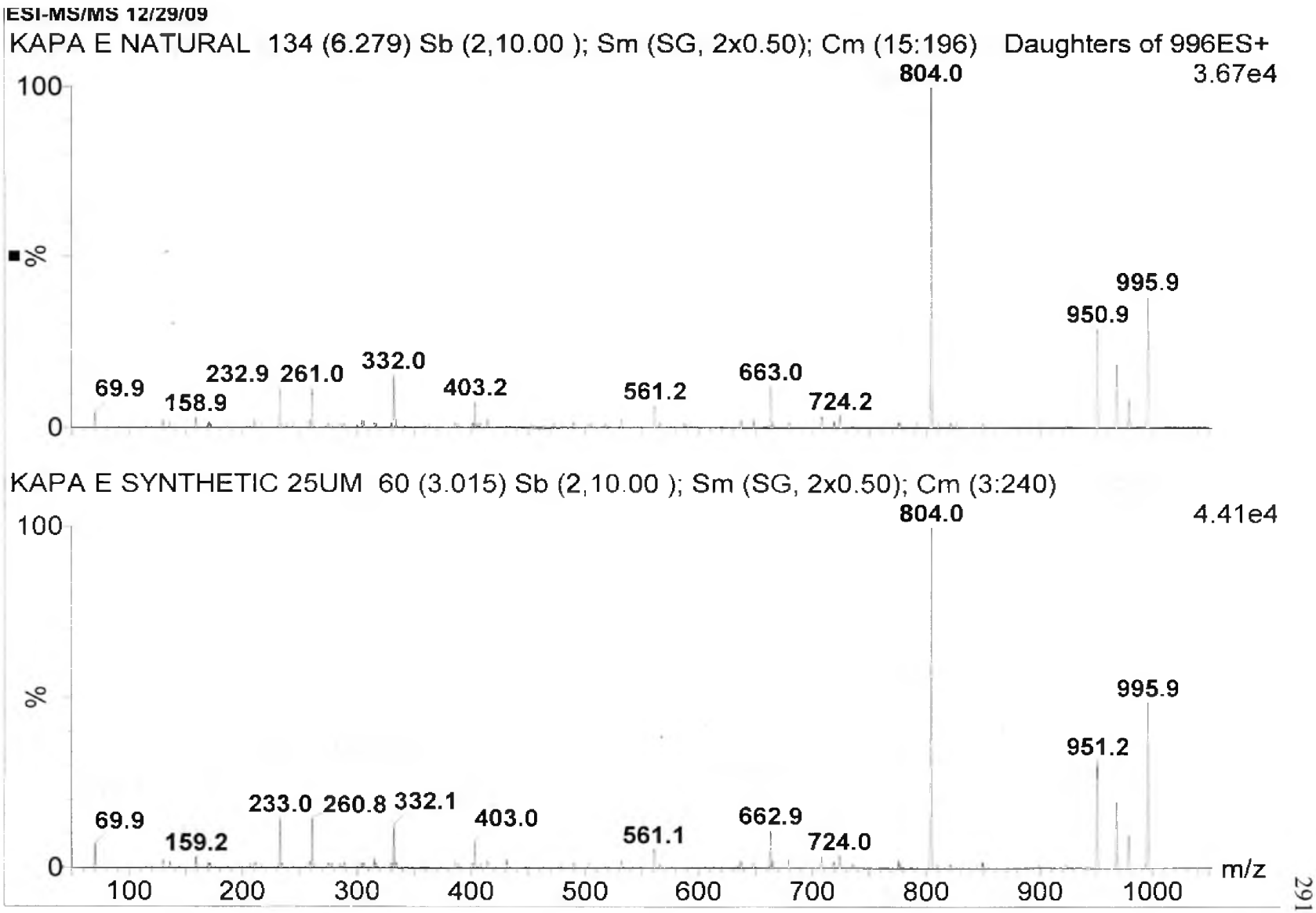
kapakahine E (**2.4**)
nOe, 500 MHz, CD_3CN
irradiation of H-9


Ph
HN
N
O
H2N
O
O
NH
O
Me
NH
H
N
(H-4)
N
H
H
O
N
N
O
OH
O
Ph
kapakahine E (2.4)
nOe, 500 MHz, CD3CN
irradiation of H-4
3.598
3.569
4.658
7.782
8
7
6
5
4
3
2
1
ppm

HPLC Coinjection of Kapakahine E

LC-MS/MS (monitoring masses 996.4 and 804.0)
Using a Waters Sunfire dC18 (3.5 µm, 2.1 x 150 mm) eluting at 0.2 ml/min with a gradient starting at 10% acetonitrile/water (0.1% formic acid) and concluding at 99% acetonitrile/water over 30 minutes.




ESI-MS/MS 12/29/09
KAPA E NATURAL 134 (6.279) Sb (2,10.00); Sm (SG, 2x0.50); Cm (15:196) Daughters of 996ES+
3.67e4
100
%
0
804.0
995.9
950.9
69.9
158.9
232.9
261.0
332.0
403.2
561.2
663.0
724.2
KAPA E SYNTHETIC 25UM 60 (3.015) Sb (2,10.00); Sm (SG, 2x0.50); Cm (3:240)
4.41e4
100
%
0
804.0
995.9
951.2
69.9
159.2
233.0
260.8
332.1
403.0
561.1
662.9
724.0
m/z
100
200
300
400
500
600
700
800
900
1000

Synthetic Kapakahine F

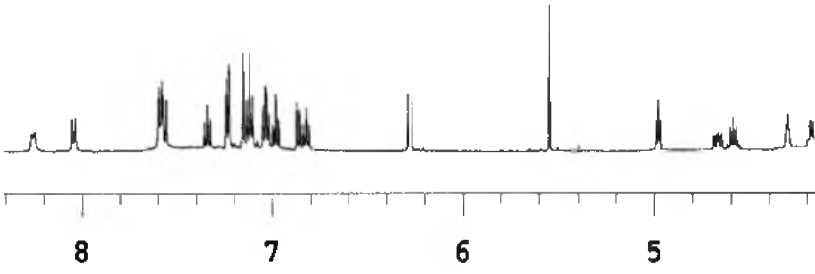
500 MHz, CD_3CN: CD_3OH:AcOH (200:100:1)

Baran, *J.Am.Chem.Soc.* 2009, *131*, 6360

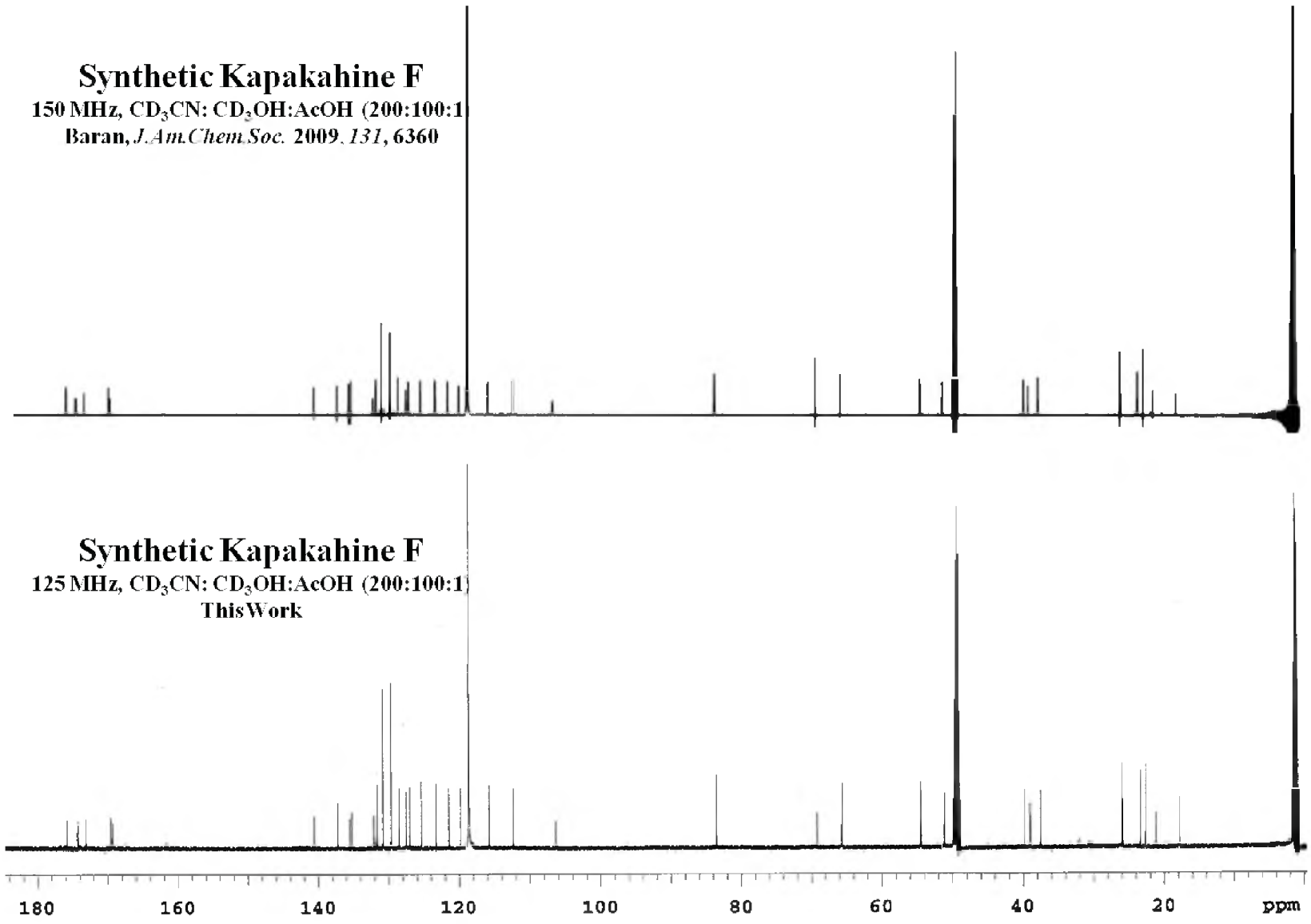
Synthetic Kapakahine F

500 MHz, CD_3CN: CD_3OH:AcOH (200:100:1)

This Work



4
3
2
1
ppm


Synthetic Kapakahine F
150 MHz, CD3CN: CD3OH:AcOH (200:100:1)
Baran, J.Am.Chem.Soc. 2009, 131, 6360
Synthetic Kapakahine F
125 MHz, CD3CN: CD3OH:AcOH (200:100:1)
ThisWork
180
160
140
120
100
80
60
40
20
ppm

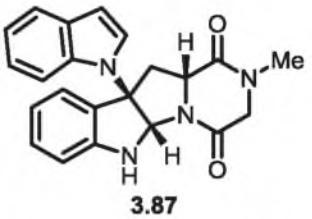
Kapakahine F - ^{1}H NMR (CD_3CN:CD_3OH:AcOH (200:100:1))	
Synthetic (this work) (500 MHz) ppm, multiplicity, *J* (Hz)	Synthetic (Baran, 2009) (500 MHz) ppm, multiplicity, *J* (Hz)
8.26, d, 7.8	8.37, bs
8.04, d, 7.8	8.04, d, 7.5
7.60, bs	7.71, bs
7.59, d, 7.8	7.59, d, 8.0
7.57, d, 8.3	7.57, d, 9.0
7.34, t, 7.3	7.33, t, 8.0
7.24, d, 7.3	7.24, d 7.5
7.15, s	7.14, s
7.12, t, 7.3	7.13, t, 7.5
7.04, t, 7.6	7.05, t, 7.5
7.04, t, 7.6	7.02, t, 7.5
6.98, t, 7.3	6.97, t, 7.5
6.86, d, 7.4	6.86, d, 7.5
6.82, t, 7.9	6.82, t, 8.0
6.28, d, 8.3	6.28, d, 8.5
5.55, s	5.56, s
4.98, t, 5.4	5.00, t, 5.5
4.67, dd, 12.8, 8.8	4.66, bdd, 12.0, 7.5
4.59, ddd, 15.2, 7.8, 7.8	4.61, bt, 7.0
4.30, dd, 3.2, 3.2	4.35, bs
4.18, dd, 13.3, 7.0	4.21, dd, 14.0, 7.0
3.42, d, 3.9	3.44, bs
3.22, dd, 14.2, 4.9	3.22, dd, 14.0, 5.0
3.12, dd, 14.5, 6.0	3.13, dd, 14.0, 5.5
2.96, d, 14.6	2.95, d, 14.5
2.57, dd, 14.6, 13.2	2.58, dd, 14.5, 13.0
1.70-1.60 m	1.70-1.61 m
1.42, d, 7.5	1.43, d, 7.0
0.96, d, 6.0	0.96, d, 6.0
0.92, d, 6.0	0.93, d, 5.5

Kapakahine F - ^{13}C NMR (CD_3CN:CD_3OH:AcOH (200:100:1))	
Synthetic (this work) (125 MHz)	Synthetic (Baran, 2009) (150 MHz)
175.8	175.6
174.2	174.4
173.1	173.1
169.6	169.6
169.4	169.5
140.6	140.5
137.2	137.2
135.5	135.5
135.2	135.2
132.1	132.1
131.7	131.6
130.8	130.8
129.7	129.7
128.5	128.5
127.5	127.4
127.0	127.0
125.4	125.4
123.3	123.3
121.4	121.4
119.8	119.9
115.8	115.7
112.3	112.2
106.4	106.6
83.5	83.5
69.2	69.1
65.7	65.6
54.5	54.4
54.4	54.3
51.1	51.1
49.9	49.7
39.8	39.6
39.0	38.9
37.5	37.5
26.0	25.9
25.8	25.9
23.3	23.4
22.7	22.6
17.8	17.9

APPENDIX C

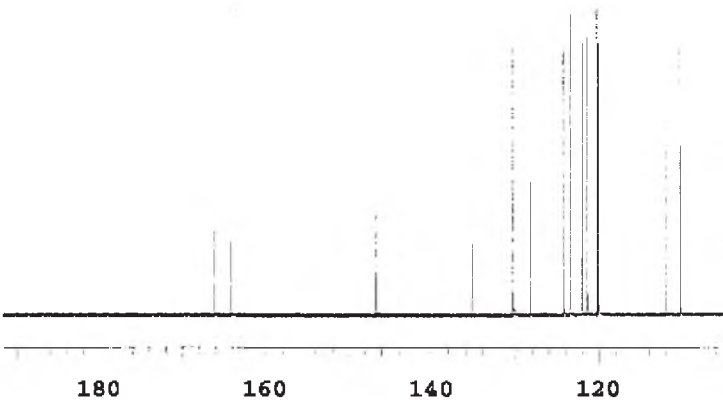
NMR SPECTRA CHAPTER 3

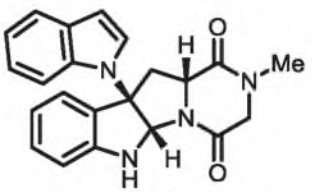

9
8
7
6
5



3.87

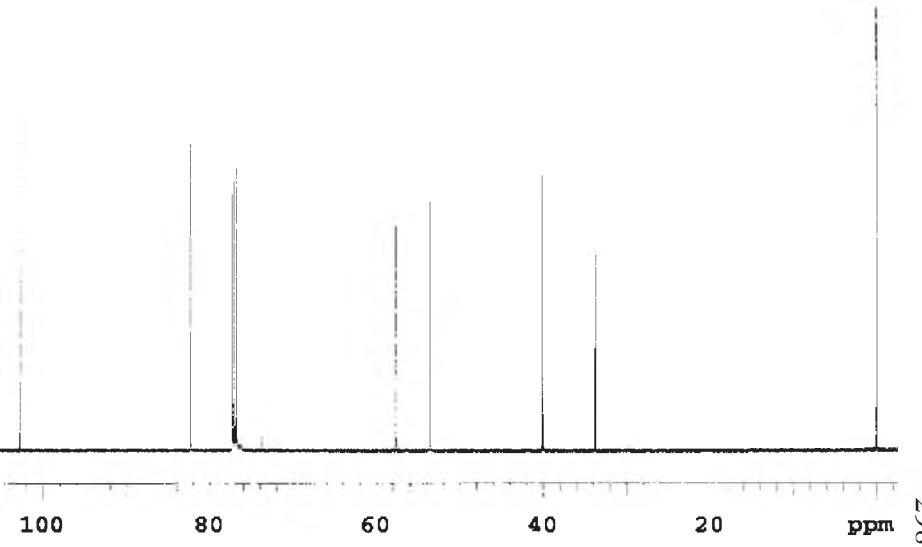
^{1}H NMR, 500 MHz, $CDCl_3$

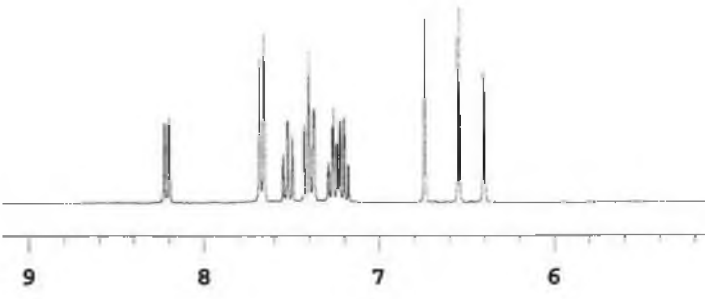

180
160
140
120

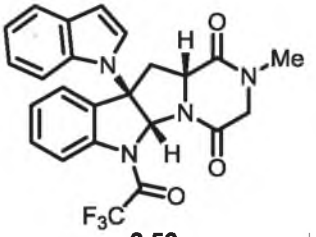


3.87

^{13}C NMR, 125 MHz, $CDCl_3$

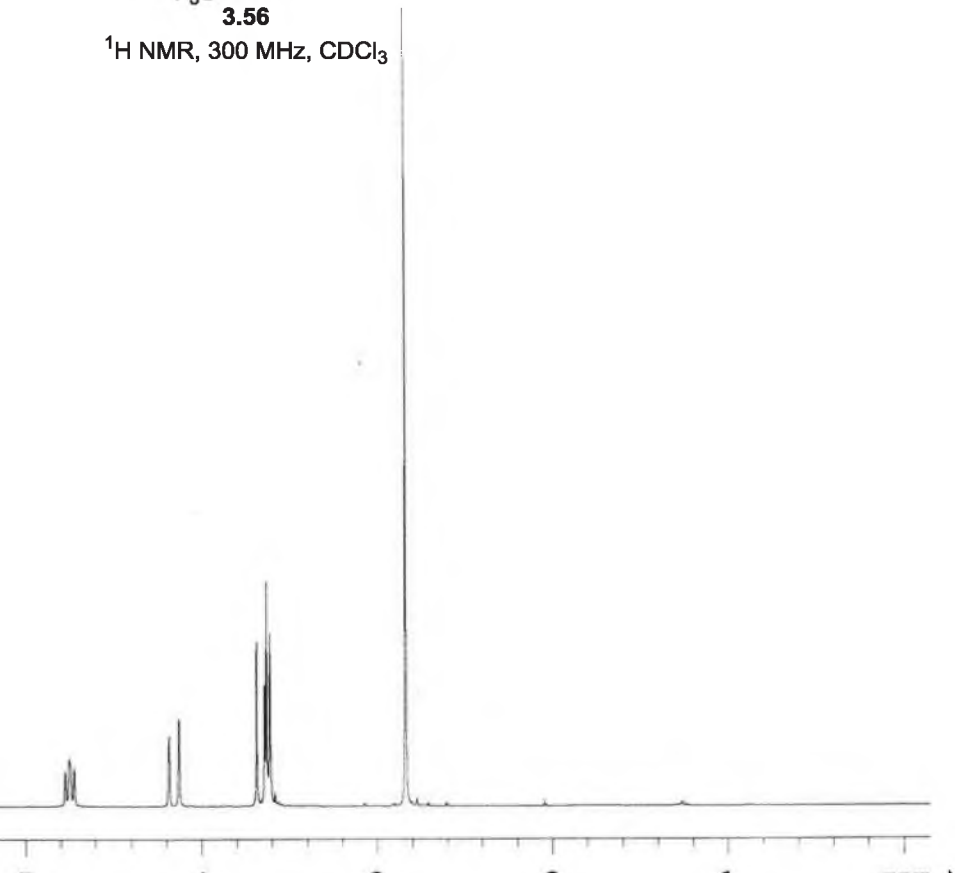


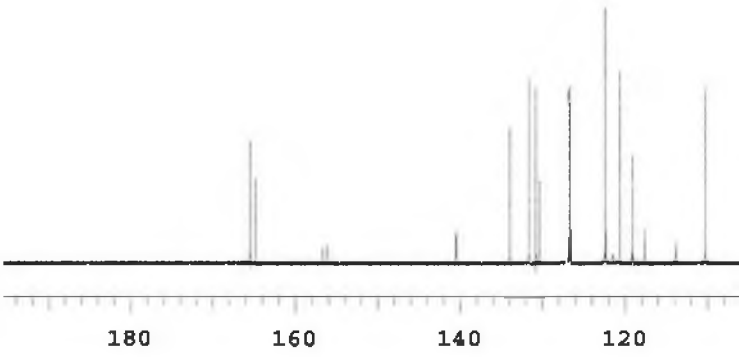

9
8
7
6



3.56

^{1}H NMR, 300 MHz, $CDCl_3$

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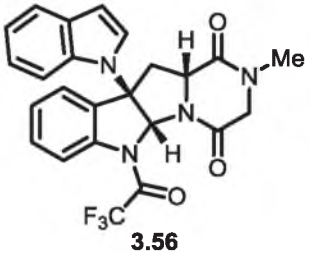
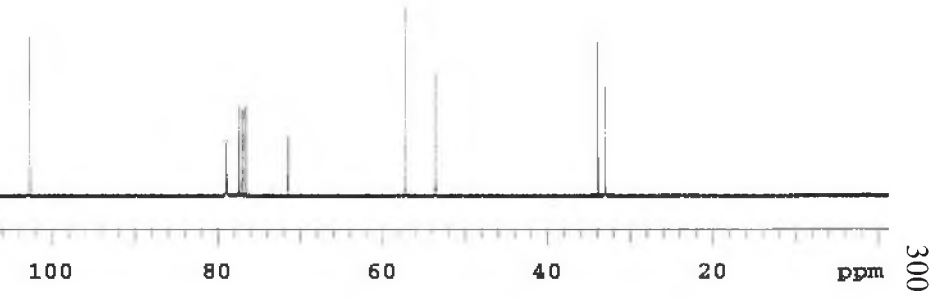
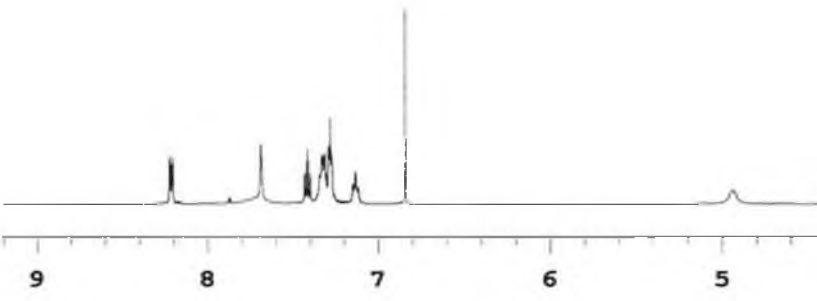


3.56

^{13}C NMR, 75 MHz, $CDCl_3$

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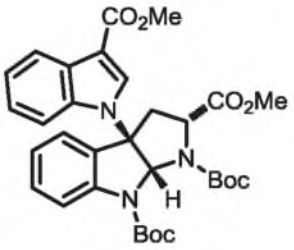
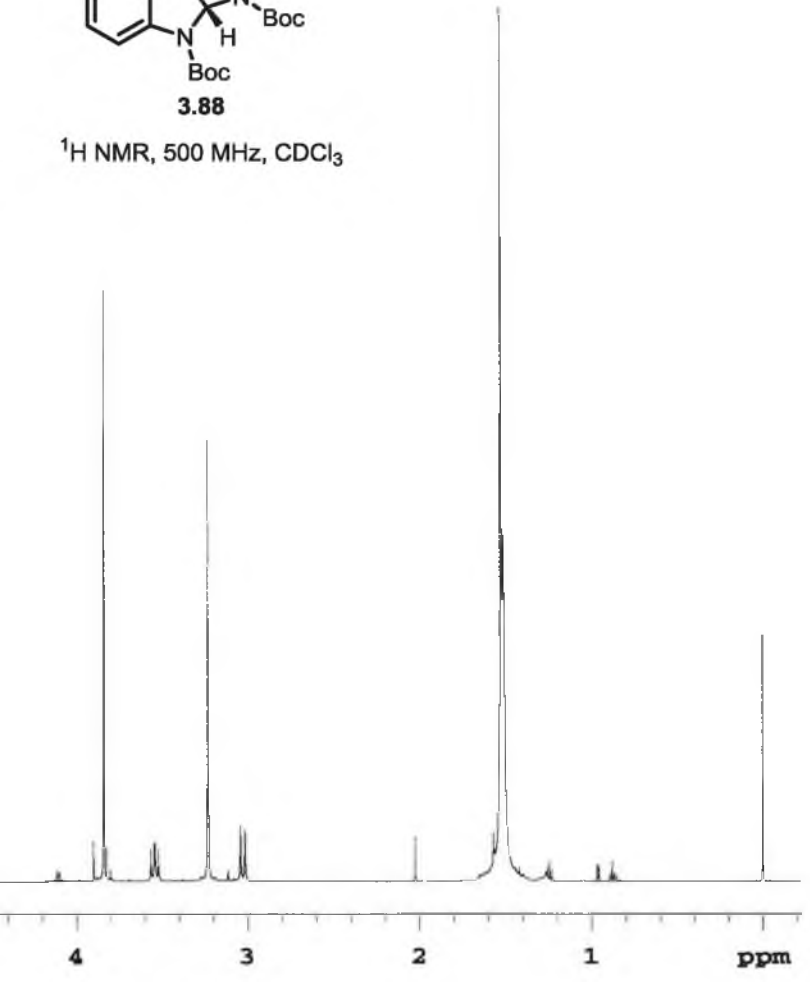
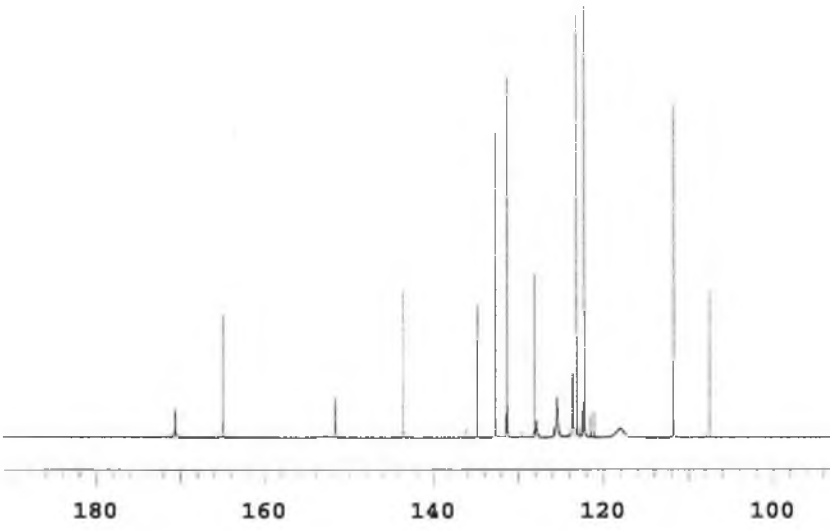


3.88

^{1}H NMR, 500 MHz, $CDCl_3$

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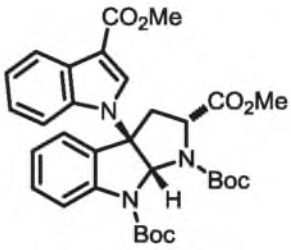
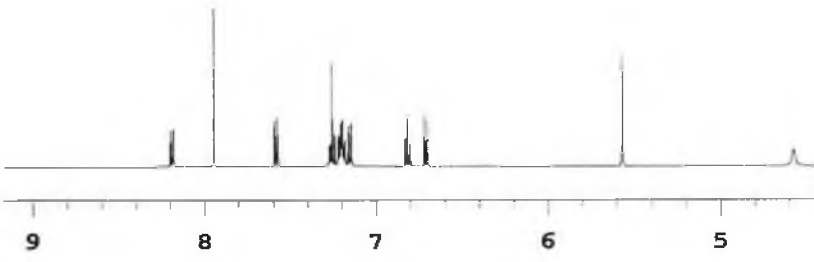


3.88

^{13}C NMR, 125 MHz, $CDCl_3$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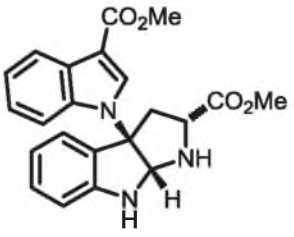
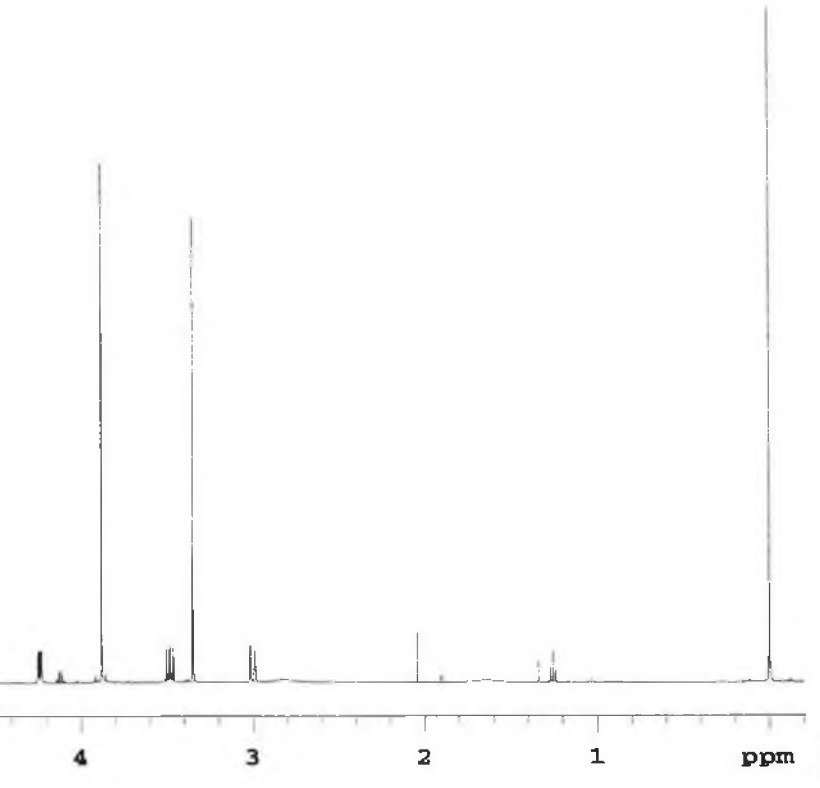
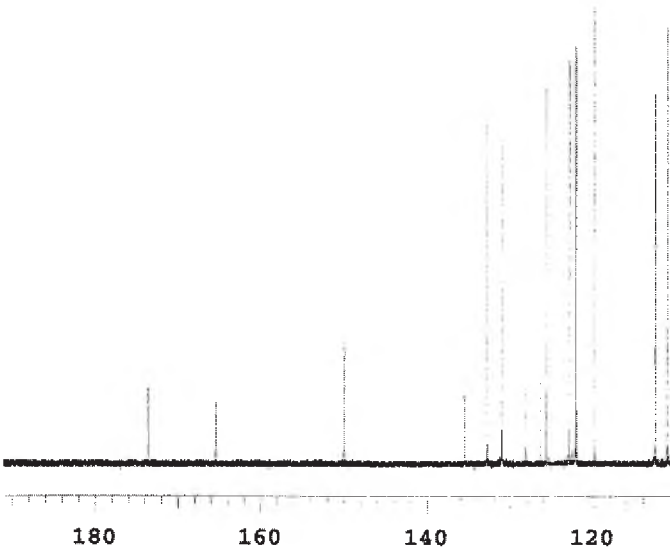


3.57

^{1}H NMR, 500 MHz, $CDCl_3$

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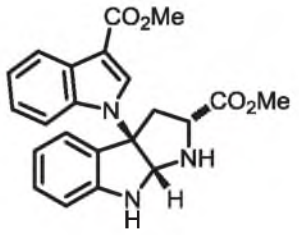
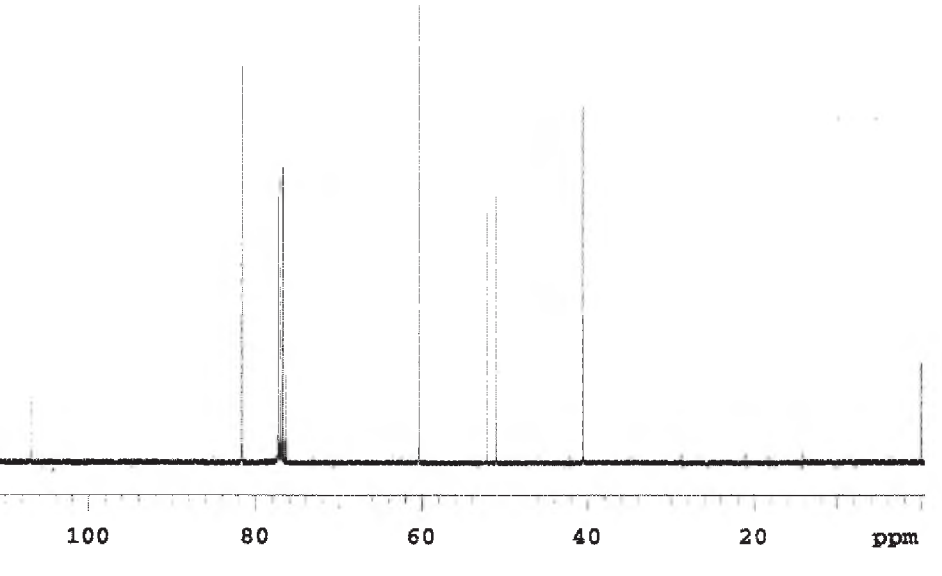
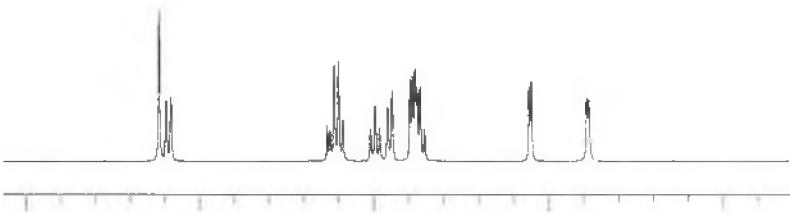


3.57

^{13}C NMR, 125 MHz, $CDCl_3$

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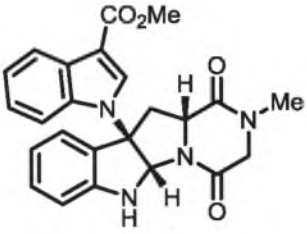
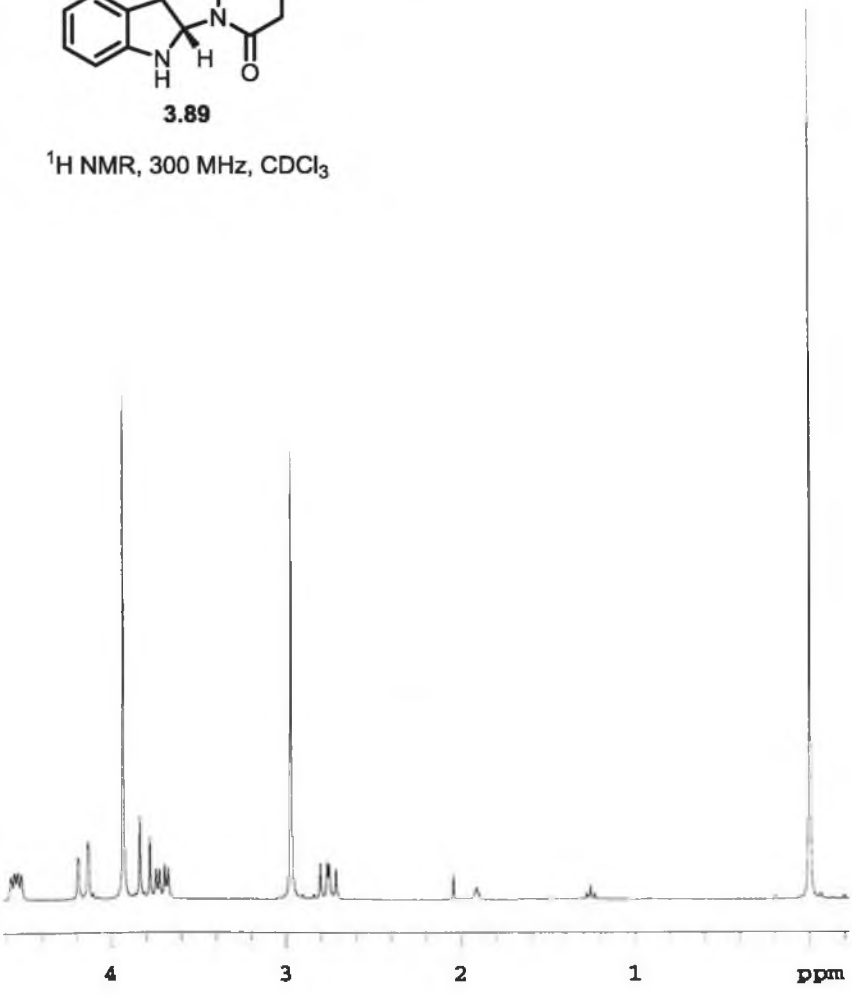
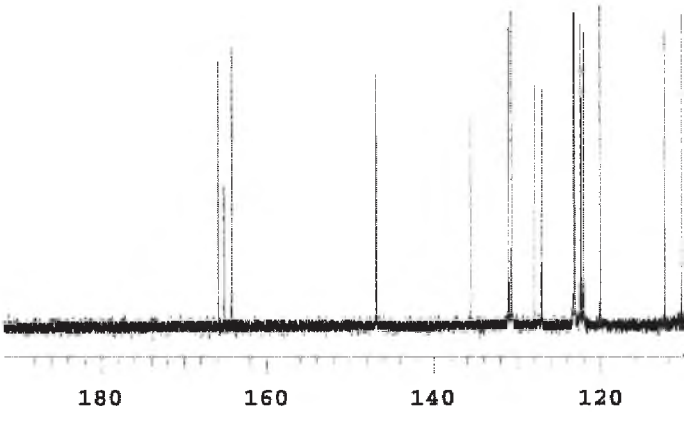


3.89

^{1}H NMR, 300 MHz, $CDCl_3$

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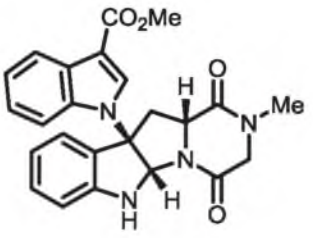
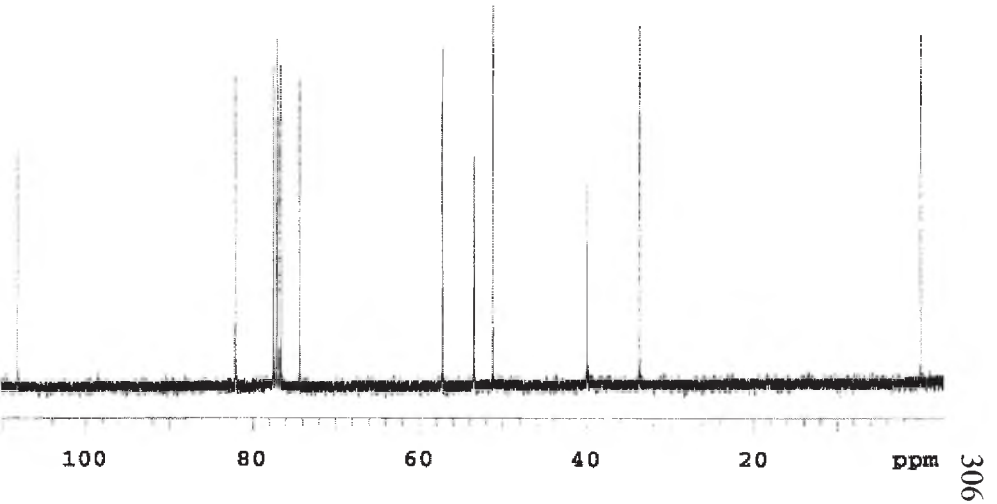
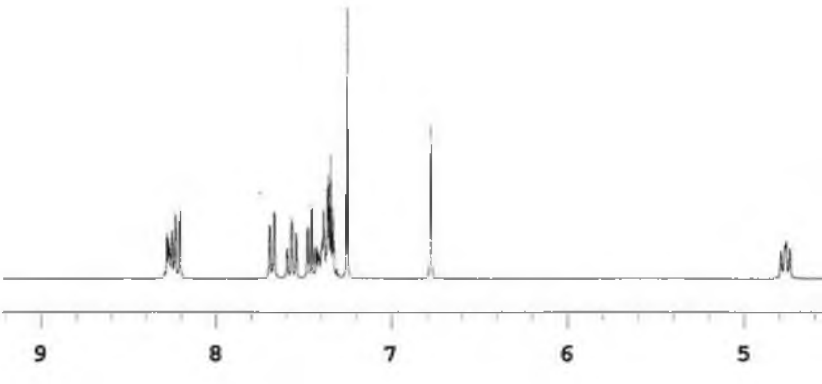


3.89

^{13}C NMR, 75 MHz, $CDCl_3$

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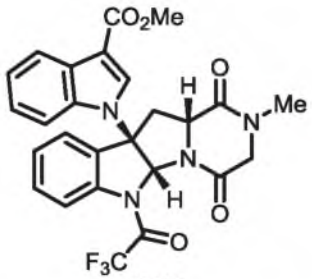
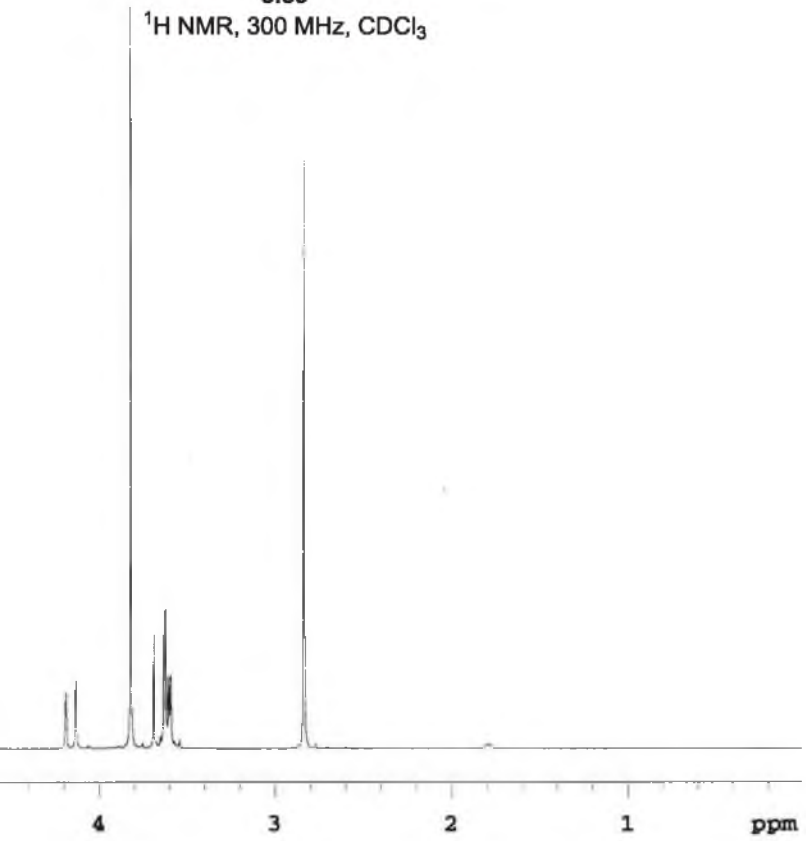
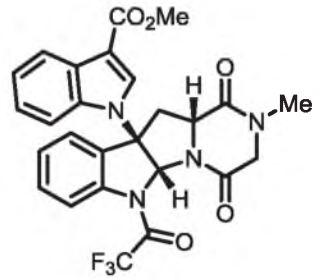


3.59

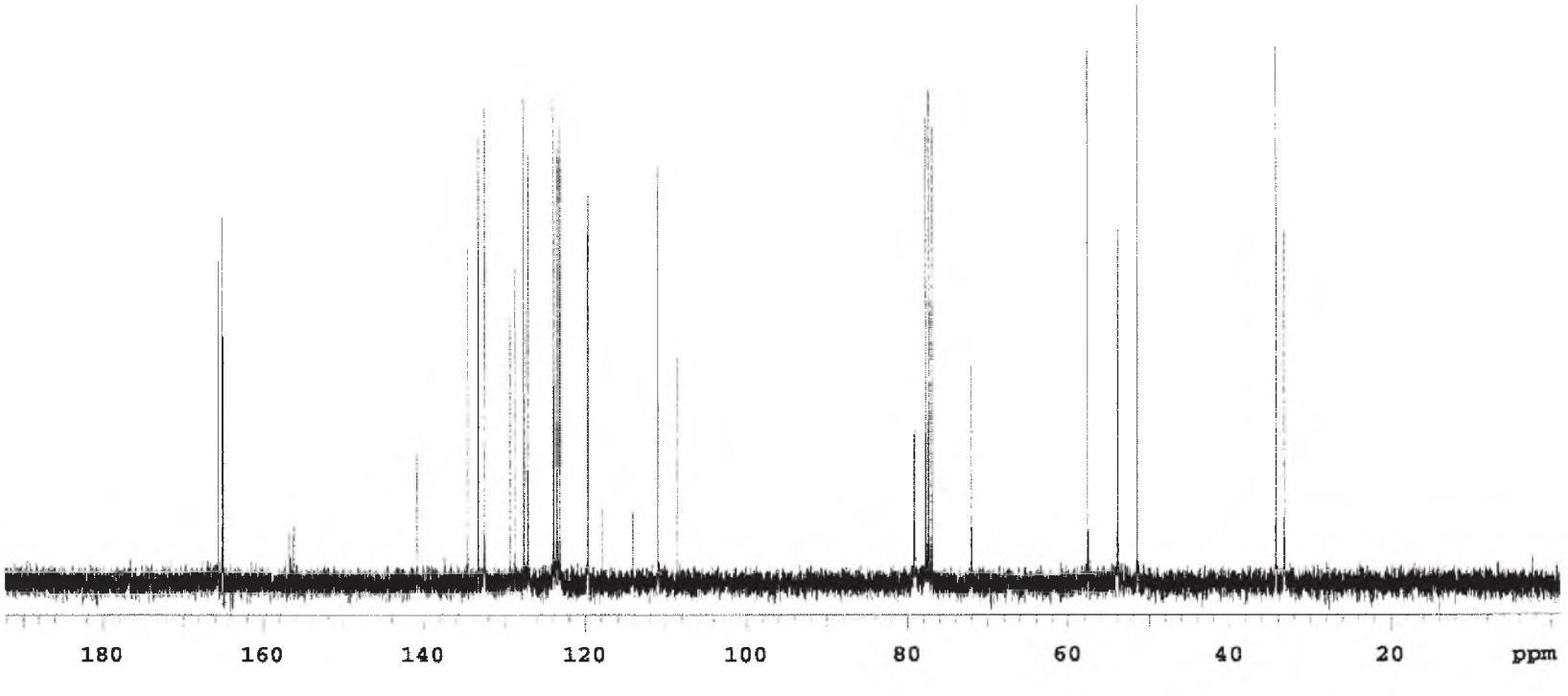
^{1}H NMR, 300 MHz, $CDCl_3$

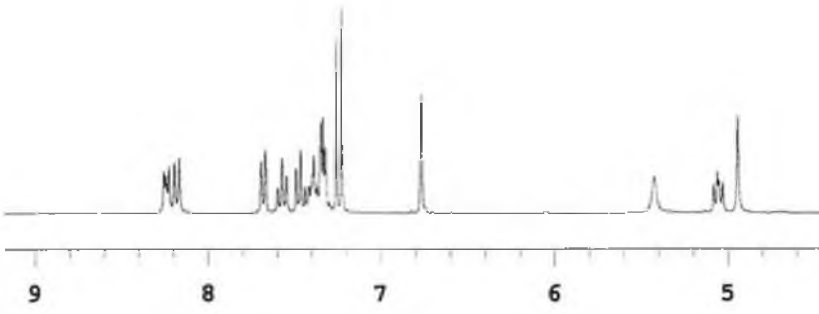




3.59

^{13}C NMR, 75 MHz, $CDCl_3$

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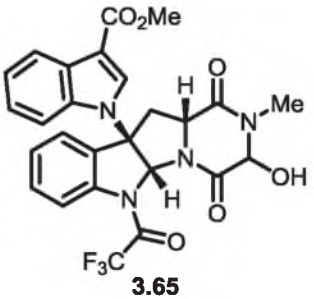
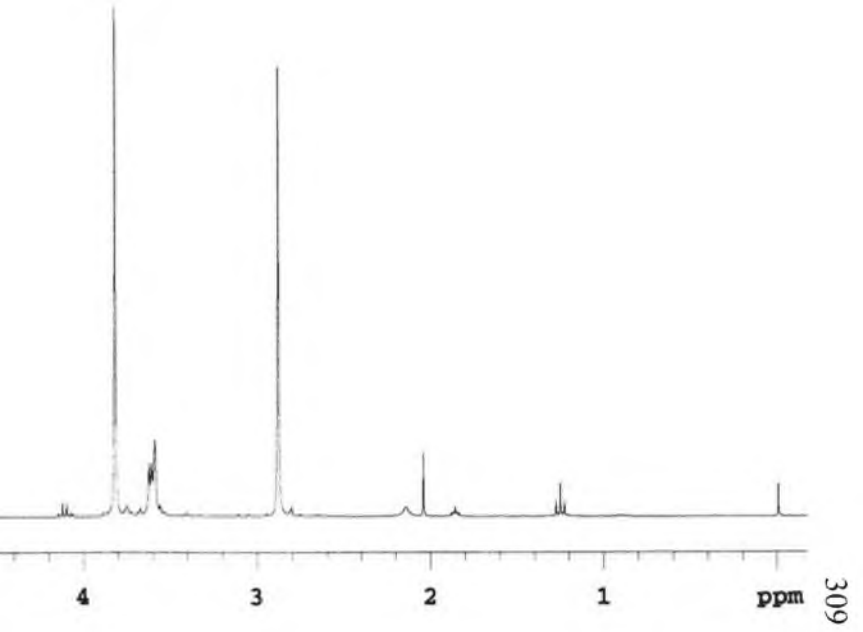
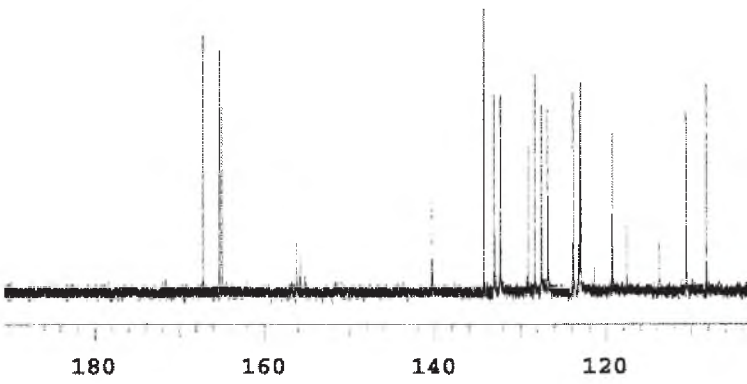


3.65

^{1}H NMR, 300 MHz, $CDCl_3$

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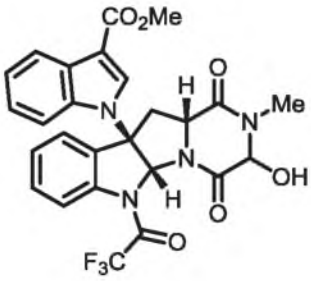
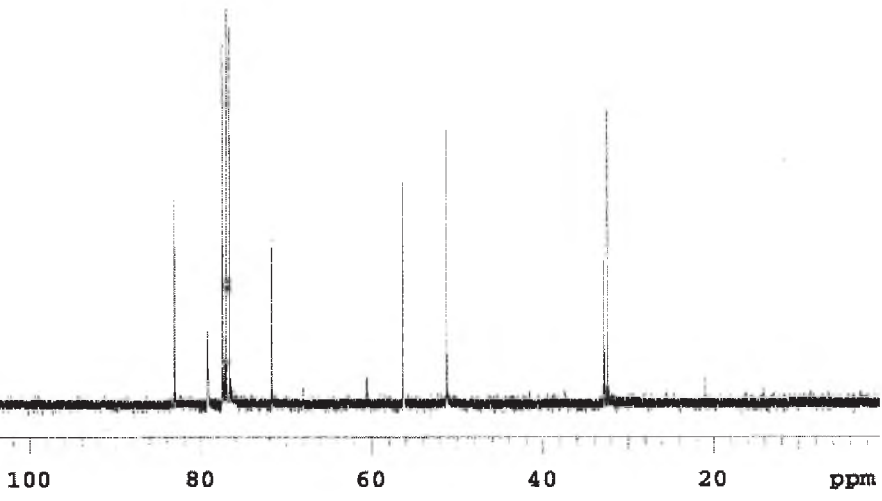
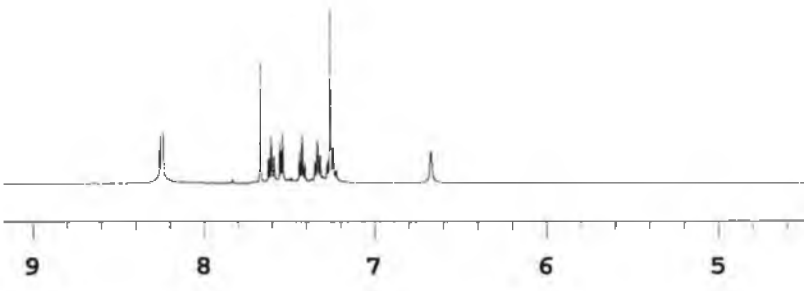


3.65

^{13}C NMR, 75 MHz, $CDCl_3$

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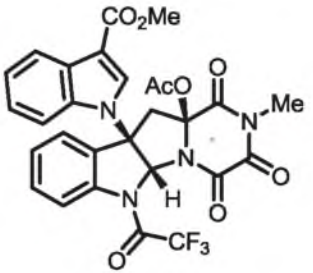
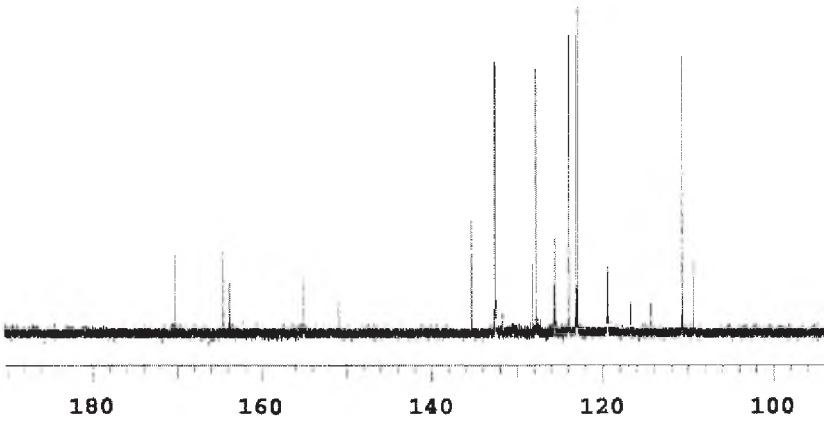


3.70-*exo acetate*

^{1}H NMR, 500 MHz, $CDCl_3$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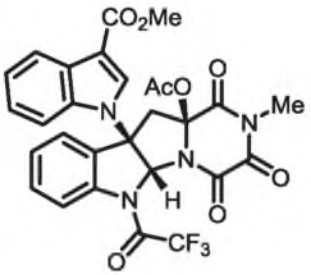
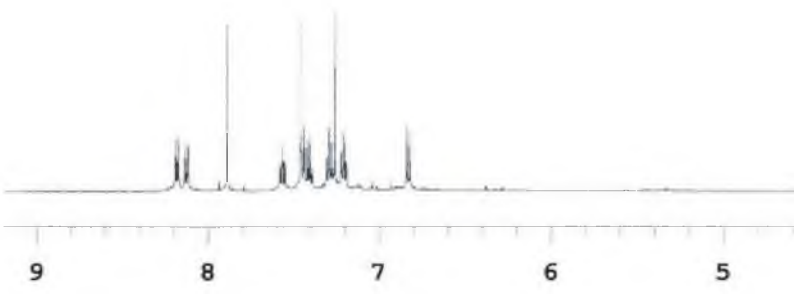


3.70-*exo acetate*

^{13}C NMR, 125 MHz, $CDCl_3$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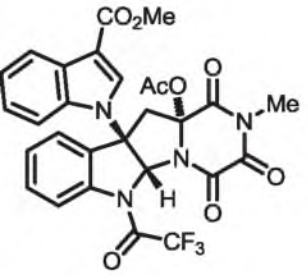
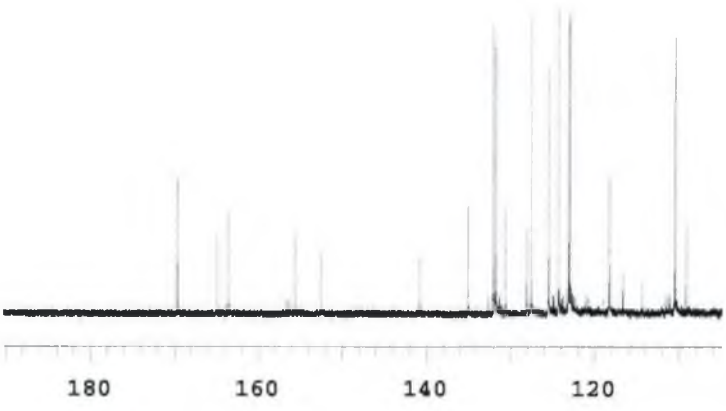


3.70-*endo acetate*

^{1}H NMR, 500 MHz, $CDCl_3$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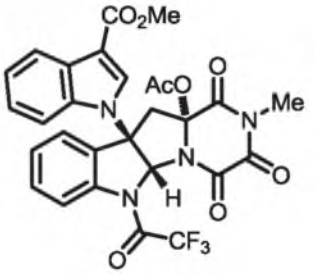
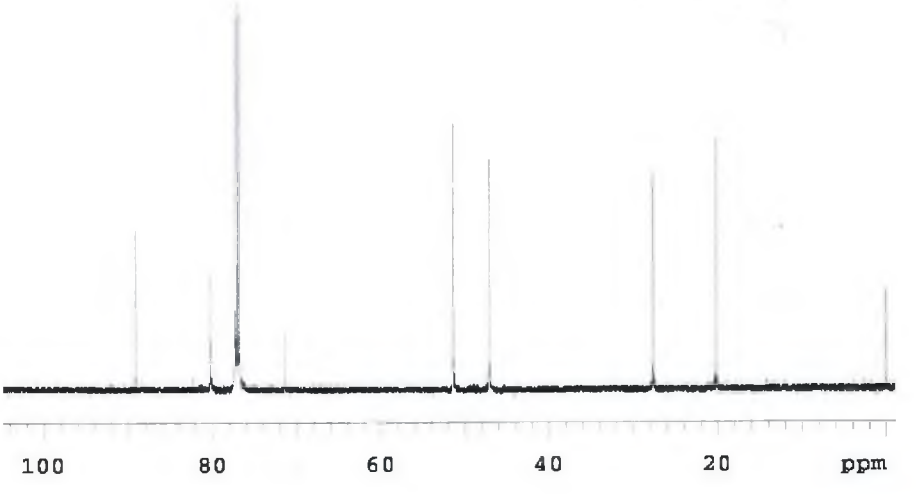
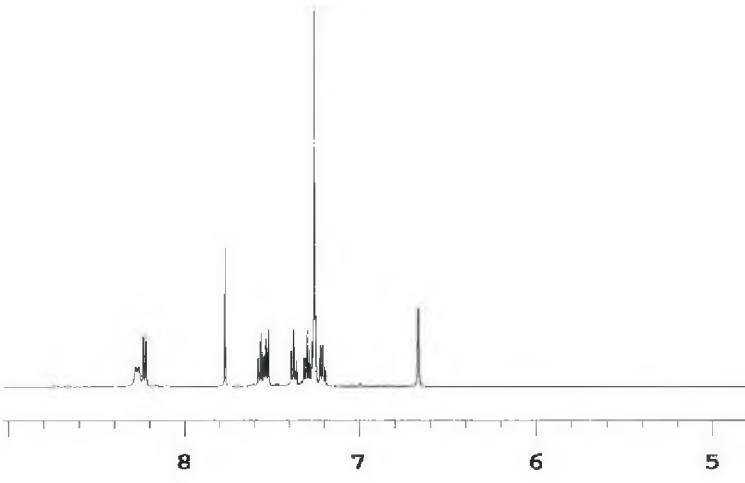


3.70-*endo acetate*

^{13}C NMR, 125 MHz, $CDCl_3$

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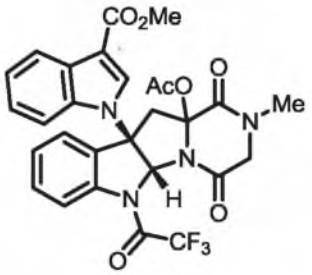
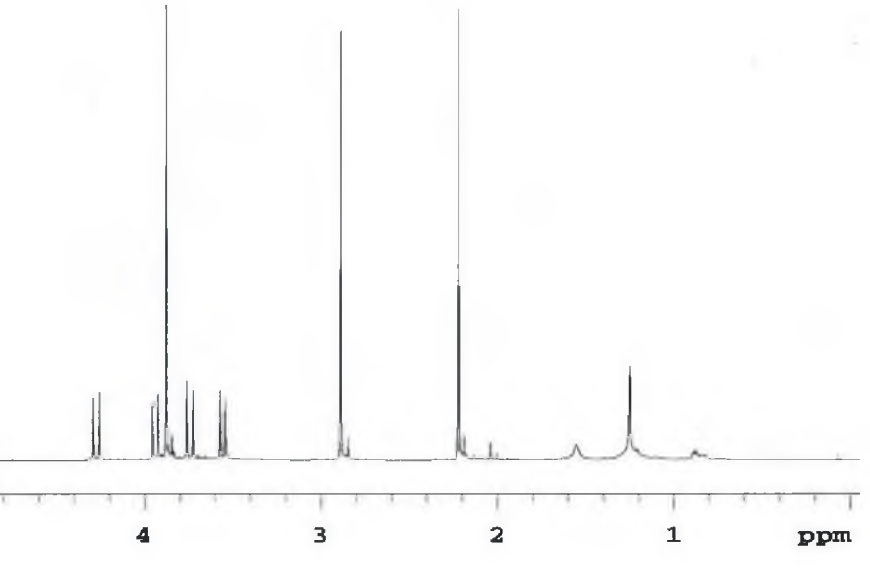
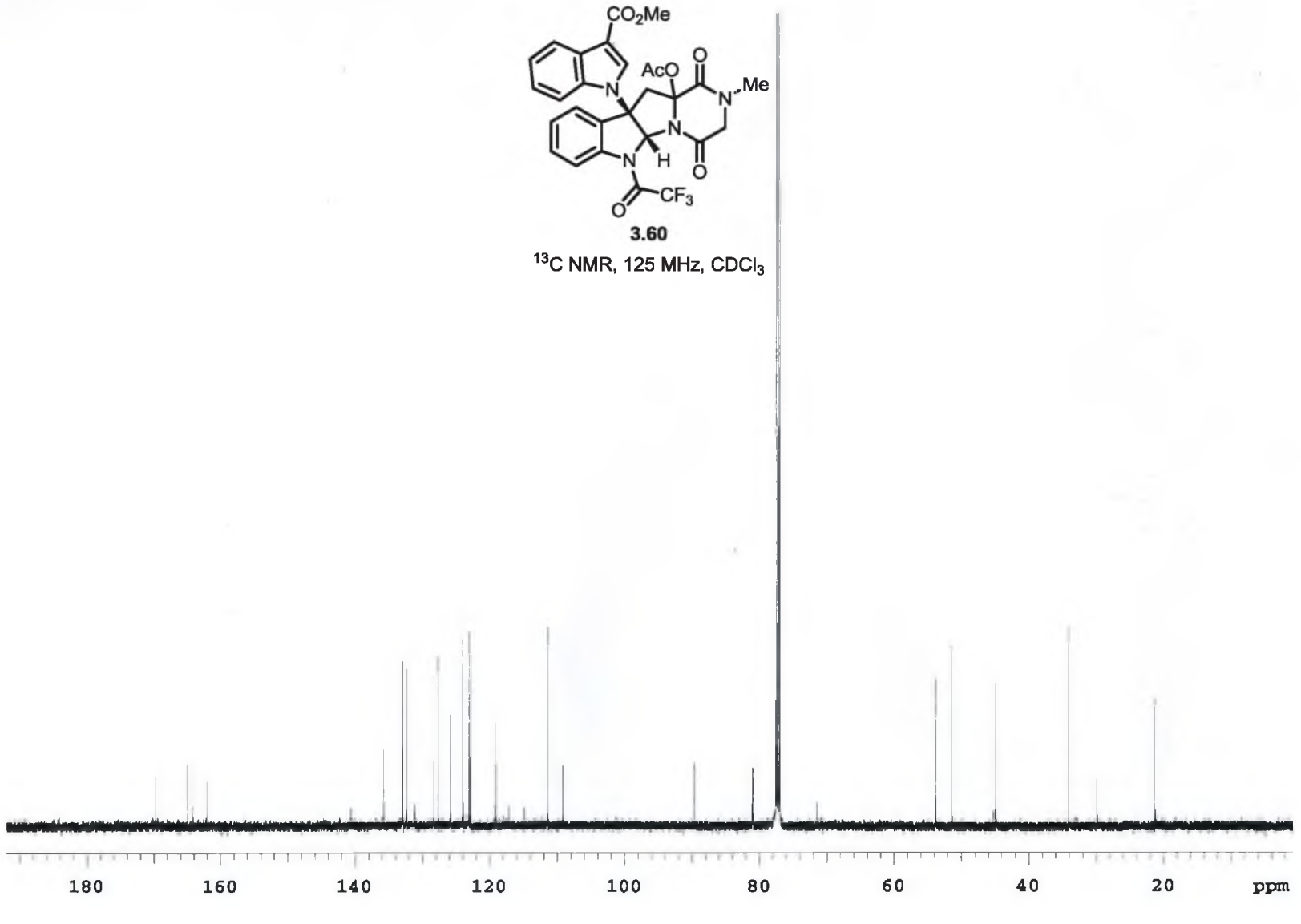


3.60

^{1}H NMR, 500 MHz, $CDCl_3$




CO2Me
AcO
O
N
Me
N
N
H
O
CF3
O
3.60
13C NMR, 125 MHz, CDCl3
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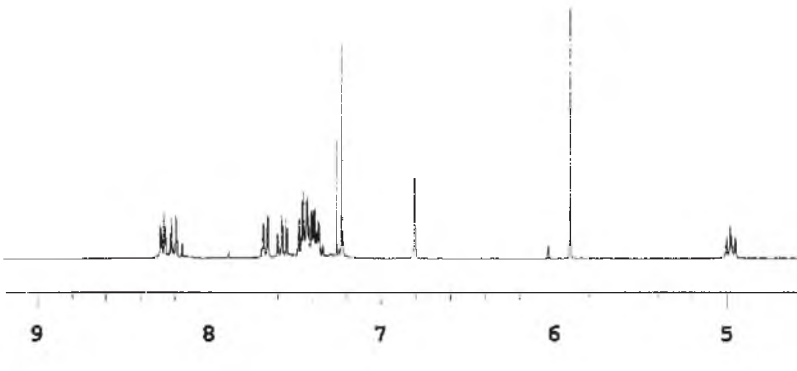
ppm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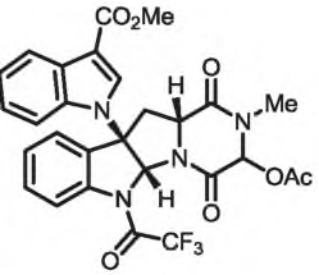
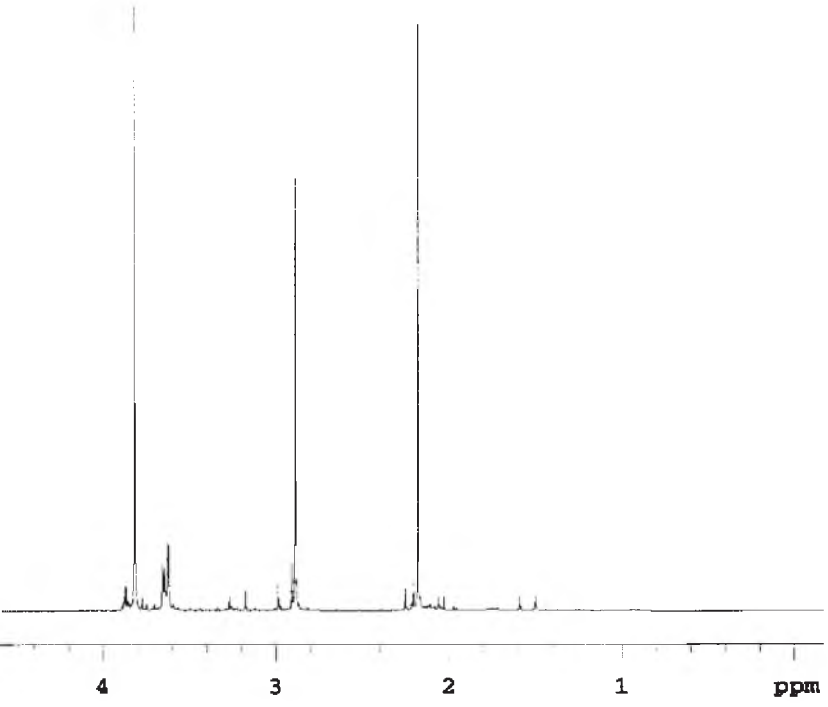
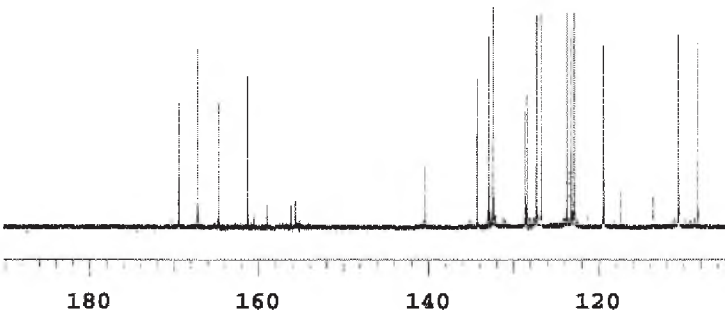


3.61

^{1}H NMR, 300 MHz, $CDCl_3$

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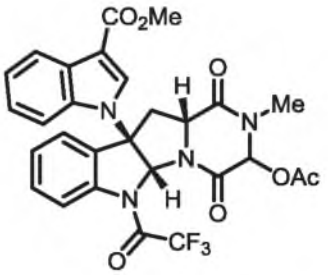
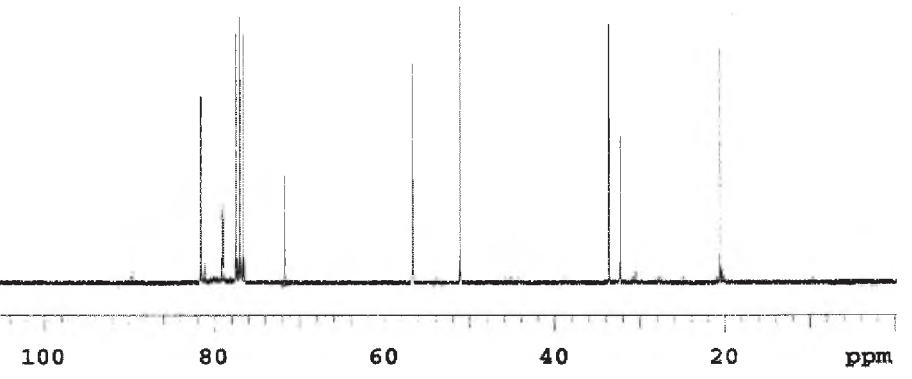
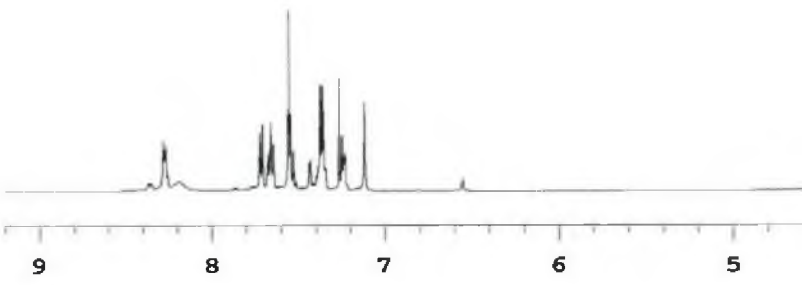


3.61

^{13}C NMR, 75 MHz, $CDCl_3$

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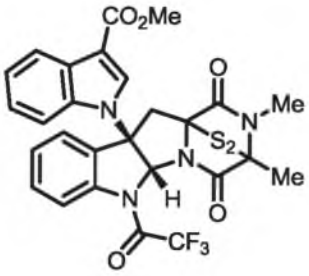
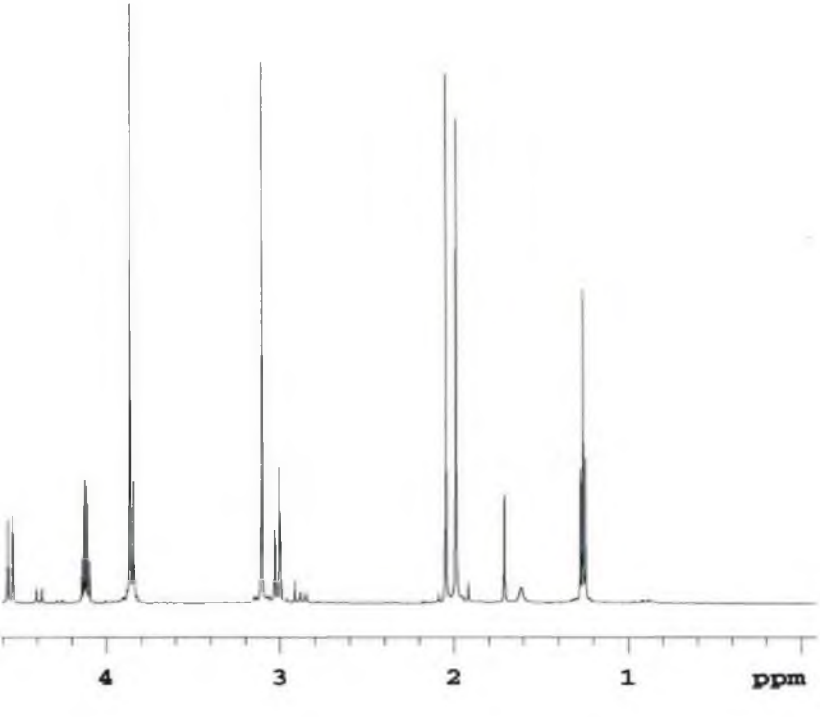
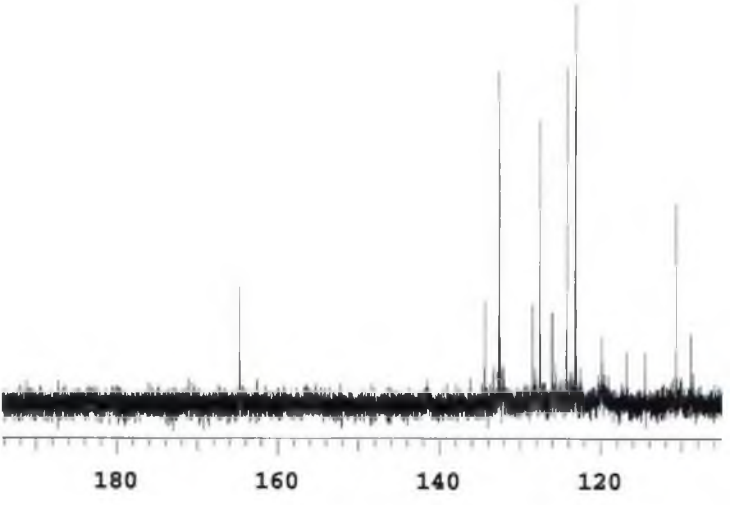
6
5

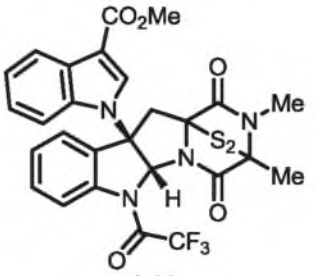


3.80

^{1}H NMR, 500 MHz, $CDCl_3$




180
160
140
120



3.80

^{13}C NMR, 125 MHz, $CDCl_3$